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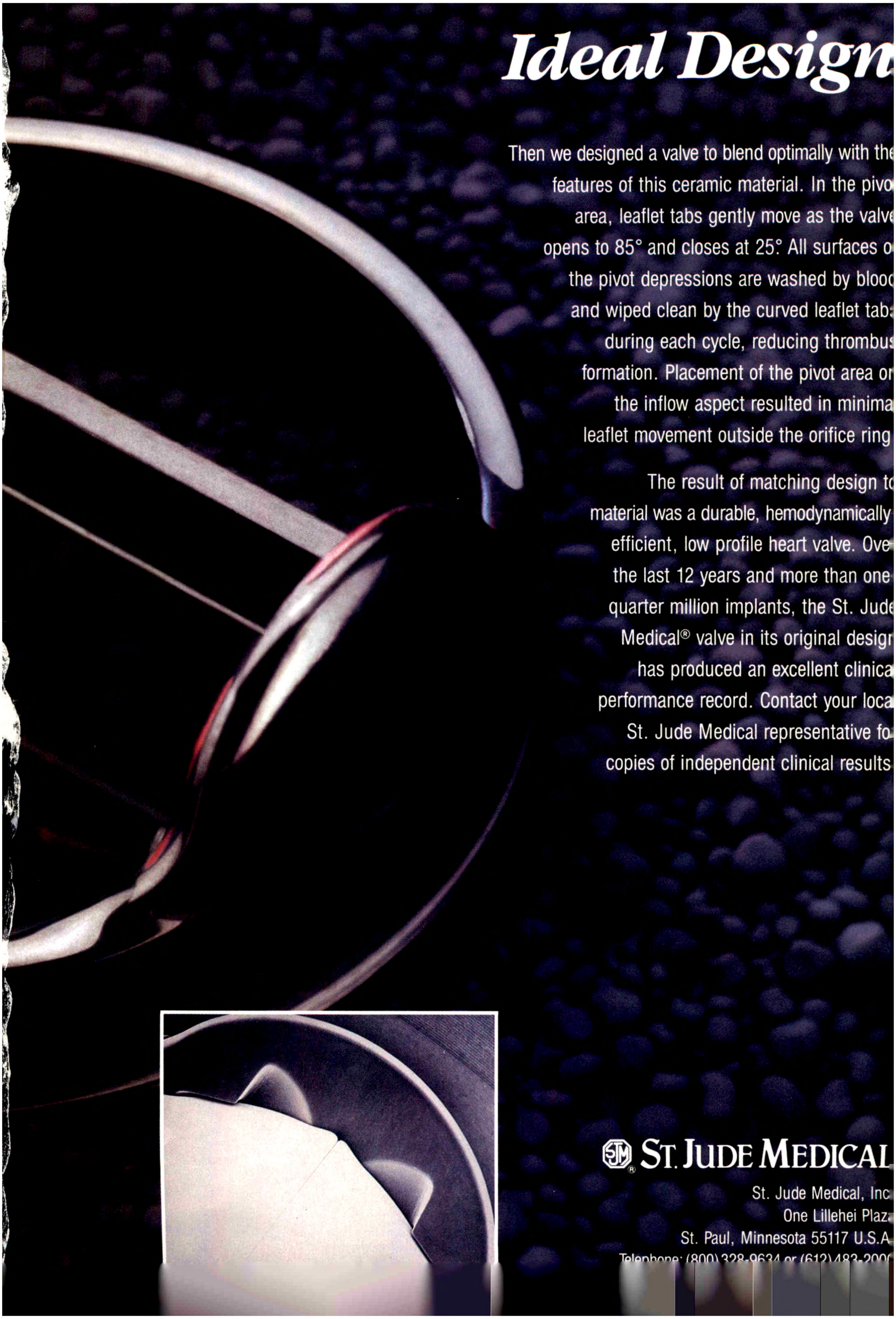

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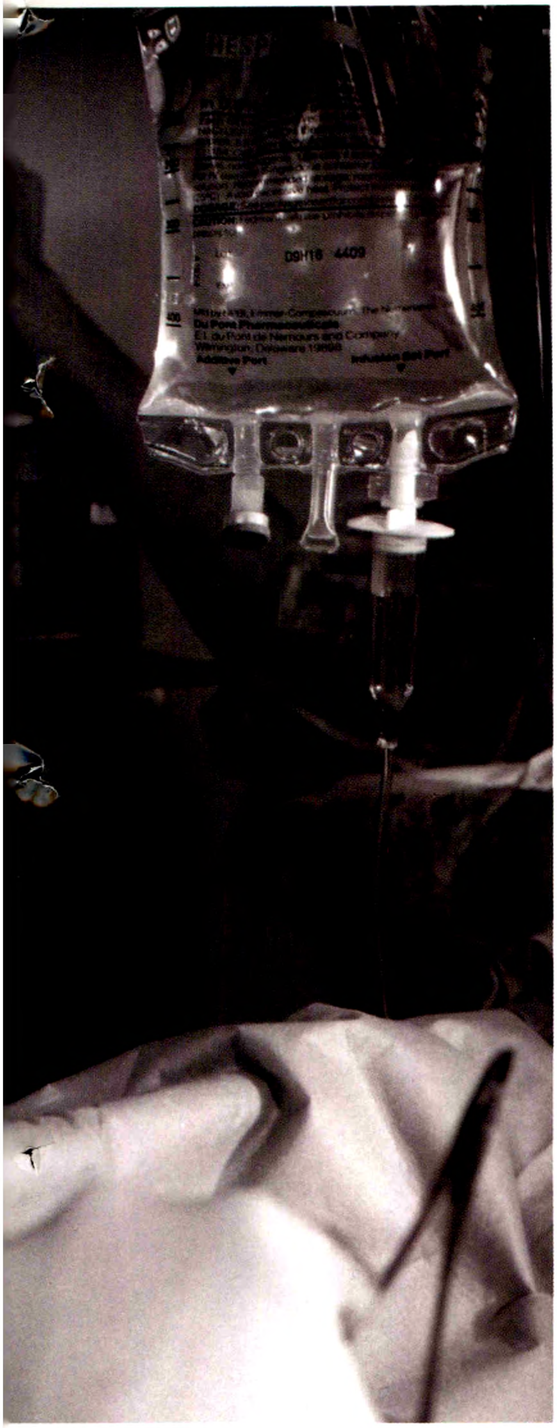

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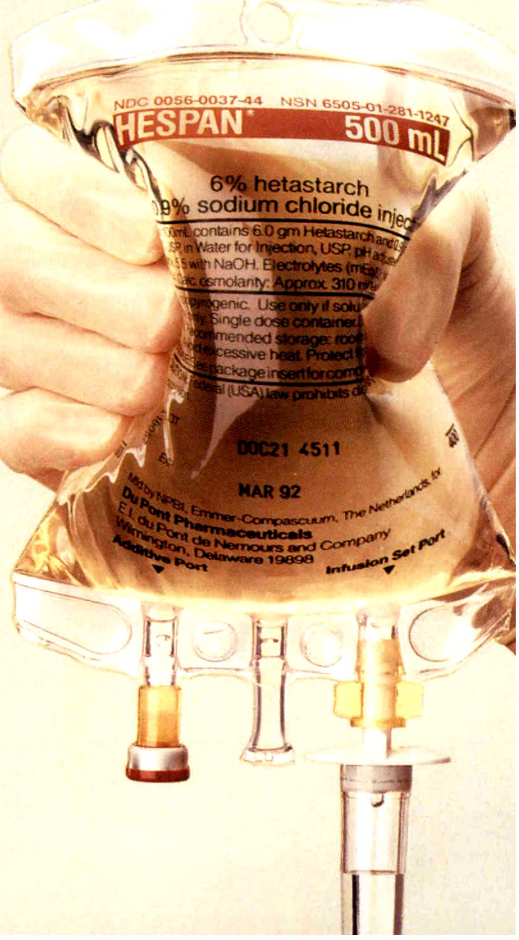
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Usage in leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of hese decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

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he possibility of circulatory overload should be kept in mind. Caution should be used when the sk of pulmonary edema and/or congestive heart failure is increased. Special care should be xercised in patients who have impaired renal clearance since this is the principal way in which etastarch is eliminated.

ndirect bilirubin levels of 8.3 mg/mL (normal 0.0–7.0 mg/mL) have been reported in 2 out of 20 ormal subjects who received multiple HESPAN infusions. Total bilirubin was within normal mits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. he significance, if any, of these elevations is not known; however, caution should be observed efore administering HESPAN to patients with a history of liver disease.

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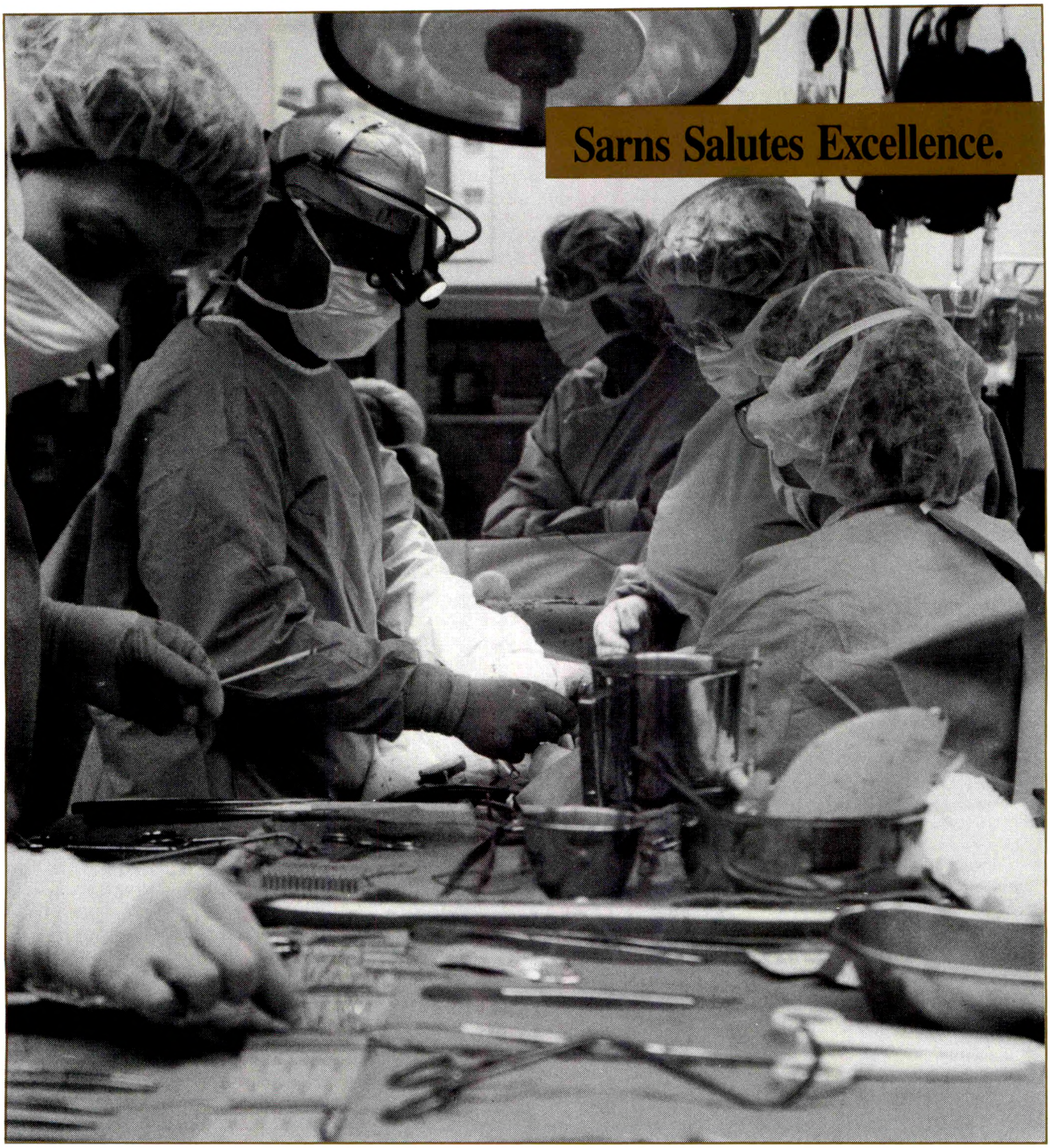
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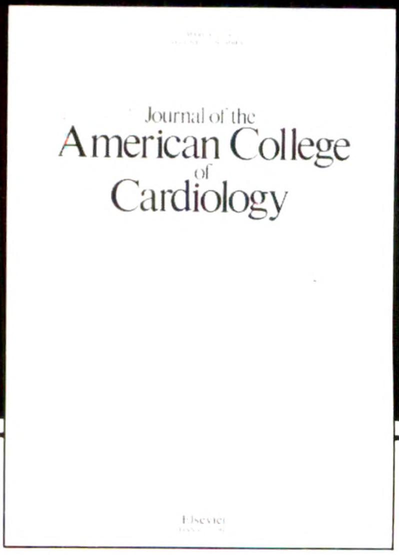

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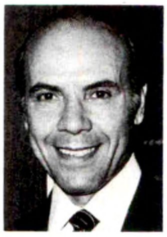
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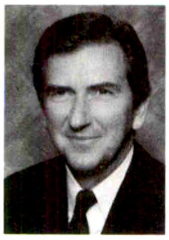
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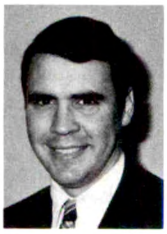
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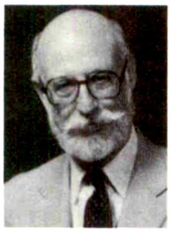

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Triiodothyronine: To Be or Not To Be, That Is the Question

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Triiodothyronine (T_3) has been suggested for the treatment of the postcardiotomy patient for more than 5 years. The initial studies, which came from Capetown, concerned brain-dead animals and patients and suggested that this hormone might be useful in cardiac and renal transplantation if given to the donor. Subsequent studies by Novitsky and associates [1, 2] in pigs and baboons placed on cardiopulmonary bypass and given global myocardial ischemia demonstrated significant efficacious effects in the former but fewer in the latter. The initial clinical data generated by this same principal investigator involved 10 cases of profound postcardiotomy low cardiac output and suggested a beneficial effect in weaning from assist devices and catecholamines [3]. No concurrent group of nontreated patients was used in that study. The more recent trial [4], which was randomized and blinded, demonstrated that patients with ejection fractions of 0.30 or less receiving coronary artery bypass operations had lower requirements for pressor and diuretic support but had no significant improvement in hemodynamic variables. Those patients with ejection fractions greater than 0.40 and given higher doses of T_3 over a longer interval (20 hours) had significantly increased cardiac outputs compared with the nontreated group, which had *normal* cardiac indices in the first 24 hours after operation [4]. The authors of that study concluded that ". . . the results . . . indicate that T-3 would be of benefit to all patients undergoing cardiopulmonary bypass for open heart surgery."

See also page 10.

In this issue Novitsky and associates [5] purport to show that T_3 is of value for the "stunned myocardium." However, they provide global data for a regional injury. There is no assurance that the drug effects reported were not the consequence of stimulation of the normal muscle rather than the ischemic-reperfused segment. The interpretation of efficacy based on the first derivative of the left ventricular pressure is fraught with hazard, especially when the two groups of animals were not similar with respect to the hemodynamic variables immediately before drug administration.

Where does this brief summary of information leave the surgeon who is called upon to treat increasing numbers of older patients with more advanced cardiac and multisystem disease, reoperative patients, and desperately sick newborns and neonates? Will the use of T_3 be of benefit to these and others who sustain varying degrees of myocardial injury during operation? Unfortunately, the data are not convincing that T_3 provides a *rapid* improvement in contractility in low cardiac output syndrome or significantly improves damaged major organ metabolism. Very few prophylactic treatments given at the onset of reperfusion have been shown to be constantly effective in terms of amelioration of injury or salutory hemodynamic effects in randomized, blinded clinical trials. If T_3 increases contractile force through the mechanisms of activation and up-regulating of adenylcyclase and adenosine phosphate translocase to improve *efficiency* of the oxidative process *without* increasing oxygen consumption, the drug may be useful for our ever-increasing group of high-risk patients.

Perhaps we are looking in the wrong place. Triiodothyronine is a potent metabolic activator of aerobic metabolism of all tissues. The striking features in the baboon and human trials were the implied effects on the kidney, water flux, and the peripheral tissues. The major effects of T_3 may well be in the noncardiac tissues that, in the very ill, markedly influence cardiac performance. Further careful animal and clinical studies of various organs and tissues will be necessary before the cardiac surgical community will accept T_3 as a silver bullet for postcardiotomy injury.

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Art and Science in the Management of Endocarditis

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Stroke is among the most devastating complications of cardiac operations, and one that surgeons make special efforts to avoid. A recent cerebrovascular accident in a patient facing a heart operation raises the concerns that cardiopulmonary bypass, and the anticoagulation necessary for it, increase the risk of extension of the infarct or conversion to a hemorrhagic stroke. Several recent series show that patients with bacterial endocarditis have a high incidence of neurologic involvement [1, 2]. Many are referred for a definitive cardiac operation for their valvar heart disease soon after a presumably embolic stroke is documented. Incomplete information guides the cardiac surgeon in the rational management of patients with endocarditis who need a cardiac operation and who have had recent cerebral infarcts.

Ting and colleagues [3], in a paper published in this issue of *The Annals*, address factors predisposing patients to stroke during and after operation for endocarditis. They have analyzed a consecutive population of 106 patients treated at the University of Illinois Hospital in Chicago and have assessed a number of factors thought to increase the risk for perioperative stroke. This useful study clearly identifies patients with a preoperative hemorrhagic infarct to be at significant risk for both perioperative progression of neurologic deficit and mortality. This important information must be one of the factors that surgeons consider in developing a therapeutic plan for these difficult patients.

See also page 18.

Certain issues are not addressed by Ting and associates. They observed a 42% incidence of preoperative stroke as detected by preoperative computed tomographic (CT) scans. Not all patients in their series, however, had preoperative scanning, and as they acknowledge, a substantial proportion of the documented infarcts were asymptomatic. The true incidence of cerebral infarction in this patient population with endocarditis therefore must be in excess of the 42% observed, consistent with the high rate of neurologic events seen by other investigators [1, 2]. Their data imply, but the authors do not suggest, that all patients with endocarditis who are facing a cardiac operation should have preoperative CT scanning if their cardiovascular condition allows. Although all of their patients with hemorrhagic strokes had symptoms, and therefore all but 1 (who was hemodynamically too unstable) had preoperative CT scans, Ting and associates would probably agree that a preoperative scan to detect hemorrhagic stroke, even in an asymptomatic patient, would be indicated.

Ting and associates make repeated reference to septic cerebral infarcts in their discussion. What, other than the fact that the infarcts occurred in the setting of endocarditis, is the evidence that these are septic rather than bland infarcts? They also noted 2 cases of postoperative cerebral abscess. Although this would certainly be evidence for septic infarction, did they examine risk factors for this complication?

Although Ting and associates aver that a CT scan is the most sensitive diagnostic test for cerebral infarction, they suggest that lumbar puncture, radionuclide brain scan, or angiogram could be done in centers where CT scan is not available. It seems inconceivable that a medical center with the capability to perform cardiac surgery would not have a CT scanner available. Both the lack of diagnostic sensitivity and the potential risks of the procedures other than CT scan suggest that these tests have only a limited role in the management of these patients. On the other hand, Ting and associates might have commented on whether a cerebral angiogram would be useful for the detection of a mycotic aneurysm in patients with documented hemorrhagic infarcts.

Ting and associates' purpose was to provide data to develop a rational plan of management of patients with endocarditis and cerebral emboli who require valve replacement. They have, however, made few specific recommendations. A reasonable extrapolation of their data suggests that a preoperative CT scan should be performed in any patient with endocarditis before a valve operation as long as the hemodynamic condition allows. Many of these patients may be asymptomatic. If a hemorrhagic infarct is detected, a delay in operation should be sought if this is feasible on bacteriologic and hemodynamic grounds. There is at present no good evidence as to how long to delay operation in this circumstance, and Ting and associates provide no new clues. Other factors such as the presence, size, and mobility of valvar vegetations detected echocardiographically may have an impact on the relative risks of delay or immediate operation. Other studies have suggested that large ischemic infarcts may also predispose to perioperative extension or hemorrhage [4]. Large preoperative infarcts also therefore may be indications to postpone operation if possible. At the least, the availability of this information preoperatively will

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allow the surgeon to provide a more accurate assessment of risk to the patient and his or her family.

Ting and associates have made a valuable contribution to the management of the difficult group of patients with endocarditis and strokes who must have an open heart operation. They have clearly demonstrated that preoperative cerebral hemorrhage is an important risk factor for the development of further perioperative neurological deterioration. Their study offers only incomplete guidance to the management of these patients and is another illustration that there is still as much art as science in their care.

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Unifocalization for Pulmonary Atresia With Ventricular Septal Defect

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In this issue of *The Annals*, Iyer and Mee [1] report their experience with the staged repair of pulmonary atresia, ventricular septal defect, hypoplastic pulmonary arteries, and systemic to pulmonary collateral arteries. Roughly, half of the patients enrolled in their protocol underwent final, complete repair of an anomaly that traditionally has been considered beyond surgical help, except for various palliative procedures. Their experience with this difficult group of patients is similar to that reported by us [2] and by Sawatari and co-workers [3]. The basic concepts used in this staged approach include (1) restoration of flow to the hypoplastic central pulmonary arteries by means of a systemic to pulmonary artery shunt or a conduit from the right ventricle to the pulmonary arterial confluence and (2) correction of arborization abnormalities of the central pulmonary arteries using pulmonary arterial segments supplied by large, discrete systemic collateral arteries (unifocalization procedures).

Indeed, our experience suggests that patients with hypoplasia of the central pulmonary arterial confluence can become candidates for complete intracardiac repair simply by right ventricular outflow reconstruction [4–8]. This maneuver appears to suffice in about 50% of the cases [7, 8]. The limiting factor in the remaining patients was limited arborization of the central pulmonary arteries.

See also page 65.

The unifocalization procedures are designed to improve the arborization pattern of the central pulmonary arteries. The use of systemic collateral arteries for this purpose required a conceptual change. In the past, these vessels were considered to be bronchial arteries with vague, ill-defined connections to the pulmonary arterial segments [9, 10]. The contributions of Haworth, Macartney, Thiene, Faller, and their co-workers [11–15] indicated that these arteries are essentially arterial conduits connecting the systemic circulation to the true pulmonary arterial segments. This allows their use for the purposes of increasing pulmonary arterial runoff from the central pulmonary arteries. Systemic collateral arteries that connect freely with the central pulmonary arteries (communicating) can be interrupted, whereas those that do not have unrestricted connections with the central pulmonary arteries (noncommunicating) must be detached from their origin, mobilized, and connected surgically to the central pulmonary arteries or their branches.

Although the report by Iyer and Mee [1] concentrates on patients with hypoplastic confluent pulmonary arteries, we have also successfully repaired patients with absent central pulmonary arteries, in whom the pulmonary arterial circulation arborization is entirely provided by systemic collateral arteries. Such cases demand staged unifocalization and prosthetic replacement of the main and unbranched portion of the pulmonary arteries [2, 15]. Similar cases were reported by Sawatari and colleagues [3].

I entirely agree with Iyer and Mee that the future of these complex surgical repairs remains uncertain. Important questions must be asked regarding the long-term behavior of conduits and anastomoses to the pulmonary arteries, and regarding the fate of the pulmonary arterioles. Although the limitations of prosthetic conduits of all types are well understood, of greater concern is the adequacy of the right ventricular decompression after complete intracardiac repair. Persistent stenosis at numerous sites of the reconstructed pulmonary vasculature often results in less than ideal peak right to left ventricular systolic ratios. In addition, there is the distinct possibility of pulmonary vascular obstructive disease affecting in variable degree the different pulmonary arterial segments. This appears as a distinct possibility owing to the uneven perfusion of the different pulmonary arterial segments. Clearly, long-term follow-up of these patients is indispensable and, when available, will be determinant in assessing the value of these complex surgical endeavors. Can these patients be better served by these techniques or by the radical procedures involved in cardiopulmonary transplantation?

Complex forms of pulmonary atresia with ventricular septal defect remain among the very few congenital heart malformations for which the search for a satisfactory surgical solution continues. Efforts such as the one described by Iyer and Mee will certainly contribute to the proper treatment of this difficult group of patients.

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Triiodothyronine in the Recovery of Stunned Myocardium in Dogs

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Two groups of dogs were subjected to a 15-minute period of regional myocardial ischemia by snaring the left anterior descending coronary artery proximal to its first diagonal branch. After release of the snare, the dogs were given either placebo (group 1: n = 7) or triiodothyronine (T_3) therapy (group 2: n = 6). The dose of T_3 given was 0.2 μg/kg at 30-minute intervals to a total of six doses. Plasma free T_3 level fell significantly during the ischemic period in both groups and continued to fall after reperfusion in group 1. In both groups, cardiac function deteriorated significantly during the period of ischemia and rapidly returned to control level after reperfusion. After 90 minutes of reperfusion, however, deterioration of left ventricular function was observed in group 1 and was significantly worse than in group 2, in which hemodynamic function was maintained and, in fact, improved to levels superior to control. It is suggested that T_3 therapy may be worthy of trial in patients in whom reperfusion of the myocardium takes place after a relatively short ischemic period (the "stunned myocardium").

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Temporary myocardial ischemia for 15 minutes in dogs induces reversible myocyte injury—the so-called stunned myocardium [1]. If blood supply to the area is reestablished, myocardial infarction will not occur. The temporary ischemia, however, leads to substantially prolonged regional left ventricular contractile dysfunction with akinesia or dyskinesia in the area at risk [2]. Associated with this mechanical dysfunction is a significant biochemical abnormality characterized by a decrease in myocardial adenosine triphosphate (ATP) and a reduction in the adenine nucleotide pool [3, 4].

For editorial comment, see page 5.

Associated with such a period of myocardial ischemia, there is a humoral and metabolic [5] response characterized by a significant increase in adrenergic activity [6] resulting in the release of endogenous and systemic catecholamines, activation of the angiotensin system, release of cortisol [7], and changes in the levels of the various thyroid hormones [7–9]. The thyroid profile is characterized by the so-called acute euthyroid sick syndrome, consisting of low plasma free triiodothyronine (FT_3), a variable level of free thyroxine, and a significant increase in reverse triiodothyronine. Levels of total triiodothyronine, total thyroxine, and thyroid-stimulating hormone remain unchanged. Similar thyroid hormonal observations have been made in other stress situations, such as myocardial infarction and cardiogenic shock [10], sepsis [11], cardiopulmonary bypass [12, 13], and after brain death [14].

We have investigated the effects of triiodothyronine (T_3) replacement therapy in a group of dogs after a period of myocardial ischemia (group 1: n = 7); the effect of T_3 on the global function of the left ventricle and on systemic and pulmonary hemodynamics has been documented and compared with the effects of placebo in a group of identically managed dogs (group 2: n = 6).

Material and Methods

Sixteen heartworm-free mongrel dogs of both sexes were used in these studies; all experimental procedures complied with the "Guiding principles in the use and care of animals" approved by the Council of the American Physiological Society.

Anesthesia

After the insertion of a peripheral venous line, a loading dose of 30 mg/kg of phenobarbital was administered. A central venous line was inserted via the jugular vein, and a continuous infusion of phenobarbital, $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, was administered throughout the experiment. After endotracheal intubation, ventilation was sustained by an Ohio Metomatic veterinary ventilator on a volume mode. Throughout the experiment, the animal received $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of normal saline solution. Arterial blood gases and electrolytes were measured at intervals and maintained within the normal ranges. At the end of the experiment, euthanasia was performed with a hypertonic KCl solution.

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Surgical Preparation

A standard lead 2 was used for electrocardiographic monitoring.

A Swan-Ganz catheter was floated through the right femoral vein into the pulmonary artery. A left thoracotomy was performed in the fifth intercostal space. The ribs were retracted, and the pericardium was incised parallel to the phrenic nerve, exposing the heart, the chest remaining open throughout the experiment. Pressure monitoring catheters were inserted into the left atrium and descending aorta. All pressures were measured by a Gould-Statham physiological pressure transducer interlinked with a Honeywell Simultrace-recorder model AR-6.

The left anterior coronary artery (LAD) was identified proximal to its first diagonal branch. A No. 2 Dacron suture was passed around the LAD at this point, and the ends of the suture were introduced through a Silastic snare. A 14-gauge needle was introduced into the lumen of the left ventricle through the apex and directly connected to a pressure transducer.

Induction of Myocardial Ischemia ("Stunning")

Once the surgical preparation was completed, the animal's condition was allowed to stabilize for 30 minutes, after which control hemodynamic status was measured. The LAD was then occluded by applying tension to the snare previously placed around the vessel. The anterolateral wall of the left ventricle rapidly became cyanotic and hypokinetic-dyskinetic. The animals tolerated the 15-minute period of ischemic occlusion satisfactorily; however, at the time of reperfusion, ventricular fibrillation occurred in 8 of the 16 dogs, necessitating cardiac massage and attempted electrical defibrillation. In 5 animals, resuscitation was successfully accomplished; these dogs were included in the study (group 1, n = 2; group 2, n = 3). Resuscitation was unsuccessful in 3 dogs, which were excluded from the study.

Hemodynamic Monitoring

The following variables were monitored: (1) cardiac output, (2) heart rate, (3) systemic arterial pressure (systolic, diastolic, and mean), (4) right atrial pressure (central venous pressure), (5) pulmonary artery pressure (systolic, diastolic, and mean), (6) left atrial pressure, (7) peak left ventricular pressure, (8) left ventricular end-diastolic pressure, and (9) positive and (10) negative time derivative of pressure (dP/dt). Stroke volume, systemic and pulmonary vascular resistances, and cardiac index were calculated.

The mean cardiac output of three consecutive readings was obtained while ventilation was temporarily interrupted. Hemodynamic measurements were made before occlusion of the LAD, at the end of the 15-minute period of myocardial ischemia before release of the LAD snare, and at 10, 30, 60, 90, 120, and 180 minutes after reperfusion.

Measurement of Plasma Free T_3

Plasma free T_3 was measured using a radioimmunoassay technique (Ciba Corning Diagnostics Corporation, Medfield, MA) at the following intervals: before LAD occlusion, at the end of the ischemic period before release of the LAD snare, and at 10, 60, 120, and 180 minutes after reperfusion.

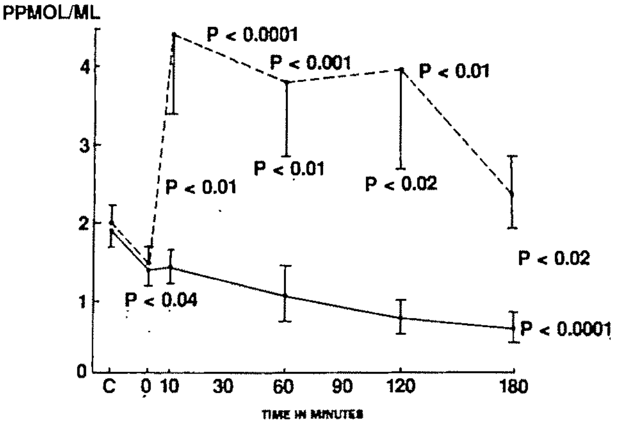

Fig 1. Plasma free triiodothyronine (T_3) levels in the placebo (solid line) *and T_3-treated* (dotted line) *dogs before, during, and after a 15-minute period of regional myocardial ischemia* (C = *control; time* 0 *indicates the time of myocardial reperfusion). Statistical differences are shown. The bars represent the standard error of the mean.*

T_3 Therapy (Group 2 Dogs Only)

T_3 (or placebo in group 1) was administered as an initial loading dose of 0.2 μg/kg 10 minutes after release of the LAD occlusion, followed by an intravenous bolus of the same dose at 30-minute intervals, for a total of six doses.

Statistical Analyses

The animals were computer-randomized into group 1 (placebo: n = 7) or group 2 (T_3: n = 6). The observer remained blinded throughout the experiment. The data were analyzed within each group by repeated measures analysis of variance and by *t* tests for unpaired data for group comparisons. A two-tail value of *p* less than 0.05 was considered significant.

Results

Plasma FT_3 level decreased significantly by 40% ($p < 0.04$) in both groups during the ischemic period (Fig 1). In the placebo group (group 1), a steady decline continued; by 180 minutes, FT_3 level had decreased a further 50%. From the time of the induction of ischemia (control) until the end of the experiment, the FT_3 level had decreased by 75% in this group ($p < 0.0001$).

A similar pattern was observed in the T_3-treated group (group 2) before the initiation of therapy, but thereafter, levels remained elevated ($p < 0.0001$) for the remainder of the experiment (see Fig 1). By 180 minutes after ischemia, the level of FT_3 was not significantly different from the control level.

There were no significant changes in hematocrit in either group throughout the experiment, indicating that hemodilution did not play a role in the decrease in FT_3.

Function of the heart deteriorated significantly in both

Table 1. Systemic Hemodynamics[a]

Variable	Control	End of Ischemia	+10 min	+30 min	+60 min	+90 min	+120 min	+180 min
CO								
Pl	3.62 (0.35)	2.73 (0.27)[d]	3.28 (0.33)	3.53 (0.33)	3.47 (0.99)	3.10 (0.29)[b]	2.81 (0.26)[d]	2.76 (0.28)[d]
T_3	3.44 (0.45)	2.44 (0.36)[c]	2.62 (0.25)[c]	3.49 (0.34)	3.55 (1.06)	3.87 (0.41)	3.89 (0.35)	3.97 (0.39)[b]
p value	NS	NS	NS	NS	NS	NS	<0.03	<0.02
CI (mL/kg)								
Pl	176 (12.8)	128 (12.5)[d]	165 (16.2)	171 (11.0)	168 (10.9)	151 (12.0)[b]	136 (9.0)[d]	132 (8.2)[d]
T_3	175 (14.7)	130 (10.5)[c]	137 (12.6)[c]	182 (16.5)	188 (25.4)	203 (22.4)	204 (18.8)[b]	205 (16.3)[b]
p value	NS	NS	NS	NS	NS	<0.05	<0.01	<0.003
HR (beats/min)								
Pl	143 (4.2)	133 (10.8)	138 (4.0)	138 (5.1)	142 (6.2)	140 (5.7)	135 (6.0)	141 (6.0)
T_3	131 (10.1)	136 (9.0)	133 (8.8)	136 (7.1)	137 (10.7)	137 (9.0)	140 (9.9)	140 (8.0)
p value	NS	NS	NS	NS	NS	NS	NS	NS
SV (mL)								
Pl	25.4 (2.26)	21.3 (2.21)[c]	24.4 (2.74)	26.2 (2.97)	25.1 (2.75)	22.7 (2.48)	21.6 (7.66)[c]	20.1 (2.38)[d]
T_3	25.7 (1.87)	18.0 (2.23)[c]	20.2 (2.30)[c]	25.7 (2.13)	26.0 (2.66)	28.7 (3.46)	28.1 (6.74)	28.4 (2.65)
p value	NS	NS	NS	NS	NS	NS	NS	<0.03
BPS (mm Hg)								
Pl	129 (7.9)	100 (8.9)[d]	111 (5.5)[c]	115 (6.0)	117 (5.0)	122 (5.1)	121 (4.0)	122 (4.0)
T_3	125 (10.0)	115 (7.1)	104 (8.4)[c]	106 (3.5)[c]	109 (6.3)[b]	115 (5.3)	113 (5.5)	114 (5.0)
p value	NS	NS	NS	NS	NS	NS	NS	NS
BPD (mm Hg)								
Pl	107 (6.7)	79 (8.5)[d]	89 (4.6)[c]	94 (6.5)	97 (4.6)	101 (4.6)	100 (3.8)	97 (4.7)
T_3	98 (9.2)	94 (7.8)	81 (9.7)[c]	86 (2.9)	85 (4.8)[b]	91 (2.8)	84 (3.6)[b]	83 (3.0)[b]
p value	NS	NS	NS	NS	NS	NS	<0.01	<0.03
BPM (mm Hg)								
Pl	117 (7.3)	88 (7.7)[d]	89 (4.6)[c]	103 (6.0)[b]	105 (4.4)	111 (4.6)	107 (3.4)	109 (12.6)
T_3	110 (7.8)	103 (7.5)	81 (9.7)[c]	94 (3.7)	95 (5.0)	101 (3.7)	95 (3.8)	96 (3.7)
p value	NS	NS	NS	NS	NS	NS	<0.03	<0.04
CVP (mm Hg)								
Pl	2.66 (0.47)	8.37 (1.92)[d]	10.00 (1.89)[d]	10.77 (1.96)[d]	9.22 (1.41)[d]	7.22 (1.02)[d]	6.87 (1.44)[d]	8.95 (2.50)[d]
T_3	3.14 (0.45)	7.33 (1.25)[d]	9.71 (1.21)[d]	5.42 (0.64)	4.00 (0.65)	4.28 (0.94)	3.42 (0.68)	2.28 (1.20)
p value	NS	NS	NS	<0.03	<0.008	<0.05	NS	<0.04
SVR (Wood units)								
Pl	34.4 (4.57)	30.7 (5.49)	30.2 (4.72)	28.6 (3.81)	29.8 (3.18)	35.5 (3.21)	38.7 (3.45)	40.0 (4.82)
T_3	34.1 (4.28)	42.2 (5.85)	25.4 (5.92)[b]	26.4 (2.30)	26.8 (1.97)	26.7 (2.79)	24.6 (2.17)[c]	25.2 (2.88)[b]
p value	NS	NS	NS	NS	NS	<0.05	<0.005	<0.02

[a] Numbers in parentheses are standard error of the mean. [b] $p = 0.05$, [c] $p < 0.01$, [d] $p < 0.001$ versus control.

BPD = diastolic blood pressure; BPM = mean blood pressure; BPS = systolic blood pressure; CI = cardiac index; CO = cardiac output; CVP = central venous pressure; NS = not significant; Pl = placebo; SV = stroke volume; SVR = systemic vascular resistance; T_3 = triiodothyronine.

groups by the end of the ischemic period (Tables 1–3; Figs 2–4), with significant decreases in cardiac output and stroke volume, and elevation of the left ventricular end-diastolic pressure. After reperfusion (and after resuscitation, when necessary) hemodynamic function rapidly returned to control level in both groups. By 90 minutes after ischemia, however, deterioration of left ventricular function was observed in the placebo group (see Table 3; Figs 2–4). Cardiac index progressively decreased (see Fig 2), and there was significant elevation of the left ventricular end-diastolic and left atrial pressures.

Hemodynamics in the T_3-treated group remained stable, and there was even some improvement above control levels during the latter part of the study (see Tables 1–3). In particular, cardiac index (see Fig 2) and dP/dt_{max} (see Fig 3) increased, and systemic vascular resistance decreased (see Fig 4).

Comment

In this study of the influence of T_3 therapy on myocardial function after a period of ischemia, we have demonstrated

Table 2. Pulmonary Hemodynamics[a]

Variable	Control	Ischemia	+10 min	End of +30 min	+60 min	+90 min	+120 min	+180 min
PAPS (mm Hg)								
PI	19.77 (2.51)	27.50 (4.76)[c]	34.12 (6.16)[c]	24.33 (2.73)	22.22 (2.09)	22.33 (2.07)	24.11 (2.47)	23.77 (2.09)
T_3	14.71 (1.96)	15.66 (1.70)	16.42 (3.49)	12.57 (2.11)	11.57 (1.60)	12.42 (1.50)	13.42 (1.60)	14.57 (2.77)
p value	NS	<0.05	<0.03	<0.006	<0.002	<0.002	<0.003	<0.02
PAPD (mm Hg)								
PI	12.66 (1.56)	18.37 (3.26)[b]	25.87 (5.67)[d]	17.00 (1.68)	15.33 (2.08)	14.11 (1.71)	15.00 (1.40)	15.88 (2.03)
T_3	7.85 (1.65)	9.83 (2.18)	9.14 (2.53)	7.00 (1.96)	6.00 (1.39)	7.00 (1.38)	7.85 (1.26)	7.28 (1.18)
p value	NS	<0.05	<0.02	<0.02	<0.003	<0.008	<0.002	<0.004
PAPM (mm Hg)								
PI	15.22 (1.86)	20.16 (2.83)[b]	29.58 (6.28)[d]	20.00 (2.02)	16.88 (1.78)	17.55 (2.05)	18.66 (1.87)	19.22 (2.22)
T_3	10.14 (1.83)	10.83 (1.56)	11.85 (2.72)	9.14 (1.85)	7.85 (1.37)	9.14 (1.45)	10.85 (1.38)	9.57 (1.30)
p value	NS	<0.02	<0.03	<0.002	<0.002	<0.007	<0.006	<0.004
LAP (mm Hg)								
PI	5.88 (1.07)	10.62 (2.28)[c]	16.75 (5.51)[d]	13.00 (2.40)[c]	10.55 (1.66)[b]	9.22 (1.59)	12.77 (2.55)[c]	13.00 (2.83)[c]
T_3	6.00 (0.87)	9.50 (2.02)[c]	10.57 (2.14)[d]	8.00 (1.48)	7.57 (1.15)	7.14 (0.85)	6.28 (1.12)	6.00 (0.57)
p value	NS	NS	NS	NS	NS	NS	<0.05	<0.04
PVR (Wood units)								
PI	2.71 (0.58)	3.58 (1.36)	4.82 (2.50)	2.26 (0.62)	1.90 (0.52)	3.05 (0.76)	2.22 (0.75)	2.31 (0.75)
T_3	1.24 (0.55)	0.98 (0.50)	0.50 (0.31)[b]	0.32 (0.12)[b]	0.78 (0.41)[b]	0.52 (0.31)[b]	1.17 (0.61)[b]	0.90 (0.41)
p value	NS	NS	NS	<0.02	<0.01	<0.02	NS	NS

[a] Numbers in parentheses are standard error of the mean. [b] $p < 0.05$, [c] $p < 0.01$, [d] $p < 0.001$ versus control.

LAP = left atrial pressures; NS = not significant; PAPD = pulmonary artery diastolic pressure; PAPM = mean pulmonary artery pressure; PAPS = pulmonary artery systolic pressure; PI = placebo; PVR = pulmonary vascular resistance; T_3 = triiodothyronine.

a significant beneficial effect of T_3 on global left ventricular function and hemodynamic response after a period of 15 minutes of regional myocardial ischemia in the dog.

The "low T_3 syndrome" is part of a nonspecific phenomenon of what is considered a general stress reaction [15]. It has been suggested that the low T_3 (or low FT_3) syndrome is a beneficial adaptive response to stress—beneficial because it results in reduced metabolic demands [16, 17]—and is accompanied by elevation of reverse T_3, which is a metabolically inactive product of thyroxine breakdown.

However, the preceding statement does not correlate with experimental and clinical observations. A rapid decrease in FT_3 and increment of reverse T_3 is associated with a high level of circulating or endogenous catecholamines; this has been observed in many acute disease states [17]. These are characterized by a progressive inability of the tissues to metabolize substrates [18], such as carbohydrates or fatty acids, most probably as a result of mitochondrial inhibition. This leads progressively toward tissue lactic acidosis and is associated with a high mortality [19]. A correlation has been shown in myocardial infarction, in which a significant reduction of the FT_3/reverse T_3 ratio is associated with a high patient mortality; therefore, what initially seems to be an adaptive mechanism, if not followed by its reversal, may become a maladaptive state, probably depending on the initial metabolic assault. Such observations have been observed in brain-dead experimental animals [20] and patients [21], during cardiopulmonary bypass [22], and during the experimental infusion of epinephrine (unpublished results). Similar changes have been documented in sepsis [23] and after major trauma [24] and operations [25].

T_3 replacement therapy to brain-dead animals leads to correction of the tissue myocardial lactic acidosis and replacement and maintenance of normal levels of myocardial high-energy phosphates; this is associated with improvement in hemodynamic function [20]. The administration of T_3 during and after cardiopulmonary bypass leads to improved cardiac function in pigs subjected to 2 or 3 hours of myocardial ischemia [26] and to increased synthesis and utilization of myocardial high-energy phosphates in baboons under identical experimental conditions [27].

After the induction of a stunned myocardium, similar neuroendocrine changes occur. There is increased sympathetic activity in the ischemic/nonischemic myocardium that eventually leads to depletion of myocardial energy reserves [28]. T_3 may act on several metabolic pathways in the myocardium. Aerobic metabolism is activated in the entire myocardium, enhancing substrate metabolism, replenishing the high-energy phosphate stores within the myocardium, and correcting the tissue lactic acidosis. The effects of T_3 on various ATPases, such as calcium ATPase, modulation of the Na/K ATPase essential for the electrical depolarization-repolarization phenomenon, and the impact on the myosin and troponin ATPases have been described [29]. T_3 has also been shown to lead to an

Table 3. Left Ventricular Hemodynamics[a]

Variable	Control	Ischemia	+10 min	End of +30 min	+60 min	+90 min	+120 min	+180 min
PLVP (mm Hg)								
Pl	127 (5.9)	104 (3.0)^d	106 (4.5)^c	144 (4.6)^b	117 (5.6)	119 (5.3)	121 (4.9)	120 (4.5)
T_3	126 (9.9)	113 (9.2)	94 (16.2)^c	104 (4.0)^c	107 (6.6)^b	113 (5.8)	113 (5.4)	113 (5.4)
p value	NS	NS	NS	NS	NS	NS	NS	NS
LVEDP (mm Hg)								
Pl	1.66 (0.60)	5.37 (1.01)^d	6.28 (0.89)^d	4.11 (1.49)^d	3.33 (1.59)^b	3.88 (1.30)^b	4.33 (1.48)^c	5.77 (0.92)^c
T_3	1.57 (0.36)	3.83 (1.42)^d	3.14 (1.33)^d	0.59 (0.89)^c	0.14 (0.50)^d	0.42 (0.39)^c	1.28 (0.94)	0.16 (0.42)^c
p value	NS	NS	NS	NS	NS	<0.05	NS	<0.02
+dP/dt (mm Hg/s)								
Pl	2,031 (822)	1,455 (239)^d	1,626 (312)^d	1,780 (310)	1,687 (235)^c	1,703 (223)^b	1,591 (232)^c	1,484 (192)^c
T_3	1,766 (189)	1,445 (272)^c	1,296 (165)^c	1,770 (259)	1,936 (257)	1,996 (261)	2,023 (266)^b	2,061 (234)^b
p value	NS	NS	NS	NS	NS	NS	NS	NS
−dP/dt (mm Hg/s)								
Pl	1,464 (189)	914 (136)^c	1,142 (53)	1,249 (105)	1,163 (137)	1,240 (88)	1,199 (65)	1,289 (123)
T_3	1,413 (21)	1,285 (185)	1,070 (205)	1,285 (428)	1,339 (382)	1,285 (428)	1,446 (375)	1,446 (350)
p value	NS	NS	NS	NS	NS	NS	NS	NS

[a] Numbers in parentheses are standard error of the mean. [b] $p < 0.05$, [c] $p < 0.01$, [d] $p < 0.001$ versus control.

+dP/dt = maximum time derivative of pressure; −dP/dt = minimum time derivative of pressure; LVEDP = left ventricular end-diastolic pressure; NS = not significant; Pl = placebo; PLVP = peak left ventricular pressure; T_3 = triiodothyronine.

increase in intracellular calcium within the cytosol [30]; this is an important component of myocardial contractility. T_3 plays an important function in catecholamine interaction and in upregulation of β-adrenergic receptors [31]. T_3 is one the major regulators of the synthesis of ventricular myosin isoenzymes [32, 33]. T_3 also controls the adenine nucleotide translocase system [34], which transports ATP out of the mitochondria into the cytosol.

Data from isolated rabbit papillary muscles have confirmed that T_3 has a major inotropic effect. This was measured by the developed tension and the maximum and minimum time derivatives of the tension. This effect was observed within 15 minutes, suggesting that this phenomenon is calcium-energy dependent and independent from DNA-RNA-protein synthesis. Beta blockers in this preparation do not inhibit this response, indicating a direct effect on the myocardium, bypassing beta receptors in a denervated isolated myocardium [35].

In an ongoing study using two sets of sonomicrometers (unpublished data) measuring the regional function of the area at risk and the normally perfused myocardium, T_3-treated animals have shown a significant functional recovery of the stunned myocardium and no major impact on the nonischemic area. In this study, T_3-treated animals

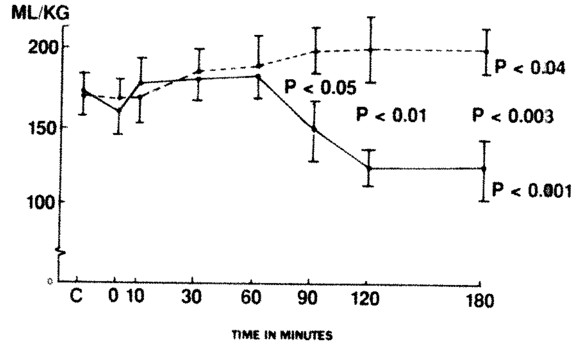

Fig 2. Cardiac index (mL/kg) in placebo (solid line) *and T_3-treated* (dotted line) *dogs before, during, and after 15-minute period of regional myocardial ischemia (C = control; time 0 indicates the time of myocardial reperfusion). Statistical differences are shown. The bars represent the standard error of the mean.*

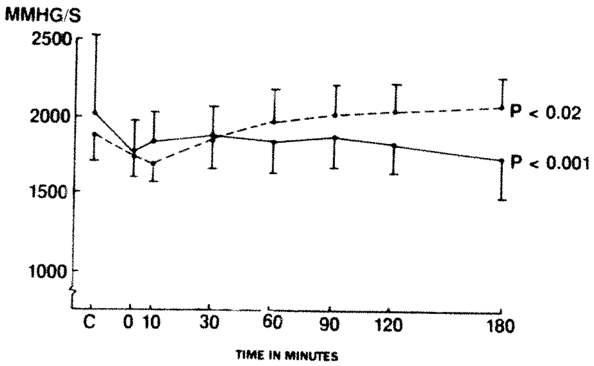

Fig 3. Maximum time derivative of pressure (dP/dt_{max}) in placebo (solid line) *and T_3-treated* (dotted line) *dogs before, during, and after 15-minute period of regional myocardial ischemia (C = control; time 0 indicates the time of reperfusion of the myocardium). Statistical differences are shown. The bars represent the standard error of the mean.*

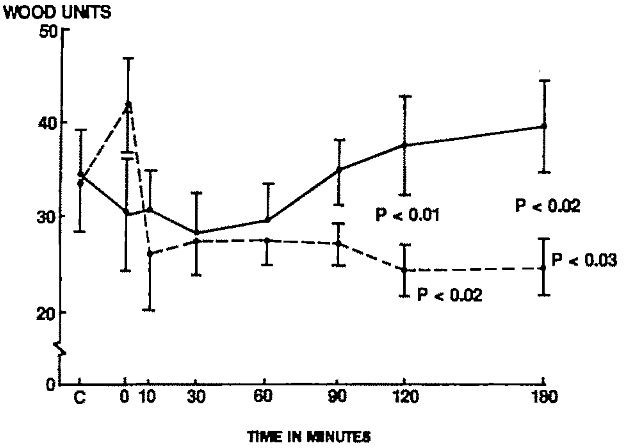

Fig 4. Systemic vascular resistances in placebo (solid line) *and T_3-treated* (dotted line) *dogs before, during, and after 15-minute period of regional myocardial ischemia* (C = *control; time* 0 *indicates the time of reperfusion of the myocardium). Statistical differences are shown. The bars represent the standard error of the mean.*

had significant recovery of the left ventricular elastance, the same as the ventricular arterial coupling. However, these variables remain depressed in the control group.

In conclusion, from the data presented in this study, we postulate that during or after the acute phase of the euthyroid sick syndrome, progressive aerobic substrate metabolism is inhibited, leading to cellular energy depletion and lactate accumulation. T_3 replacement reverses this metabolic abnormality and stimulates the aerobic pathways, probably being a major anabolic regulator of high energy phosphates increasing the cellular nucleotide pool, thus enhancing myocardial contractility. Therapy with T_3 would therefore appear to be both of theoretical and practical value in the management of patients who have undergone myocardial revascularization after a period of ischemia, such as after thrombolytic therapy, percutaneous transvenous coronary angioplasty, or coronary artery bypass grafting.

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DISCUSSION

DR WATTS R. WEBB (New Orleans, LA): I think this is an interesting paper and very stimulating. I have some questions about why levels of T_3 would decrease as a result of this. Can you go a little more into exactly the physiopharmacology that you think really happened in this situation rather than just all the things that T_3 might do? I think that we might see much the same response just from the use of nitroglycerine and nitroprusside with a major action being a reduction of the afterload and peripheral resistance. Would that alone not give the same effect as you saw here?

DR NOVITZKY: The reason for the reduction in plasma free T_3 is unrelated to hemodilution as there was no significant difference of the hematocrit within and between the groups. Tissue thyroxine conversion depends on two different monodiodinases that are probably modulated by the release of endogenous and circulating catecholamines, converting thyroxine into T_3 or reverse T_3, the latter an inactive byproduct.

The rapid disappearance of plasma free T_3 has been observed in all stress situations characterized by high cortisol and catecholamine levels, such as in cardiopulmonary bypass, myocardial infarction, and in any type of shock, eg, hemorrhagic or septic.

We have documented a positive inotropic effect on the myocardium, observing a significant dP/dt_{max} increment. The afterload reduction does influence the dP/dt but is not one of the major determinants, as the dP/dt_{max} peak occurs at the time of the aortic valve opening. T_3 may have a direct vasodilatory effect or may cause inhibition of the sympathetic drive as a result of the improvement of the cardiac output observed in this study.

DR RICHARD P. ANDERSON (Seattle, WA): As a cardiac surgeon, I have looked at more stunned myocardium than I care to recall. By looking at the heart, could you tell whether you had given a placebo or had given a drug?

DR NOVITZKY: You mean during bypass, during the open heart operation?

DR ANDERSON: In your preparation. Is it closed chest?

DR NOVITZKY: This is an open chest model.

DR ANDERSON: So you have open-chested dogs and you are giving some of them a placebo and some of them a drug, right?

DR NOVITZKY: Yes.

DR ANDERSON: And you are looking at the heart, right?

DR NOVITZKY: Yes.

DR ANDERSON: Okay. Does the heart look different in those that received placebo versus those that received blood?

DR NOVITZKY: Initially no differences were observed in the performance of hearts from both groups, such as during the ischemic time (during the 15 minutes of LAD occlusion). Once coded medication was administered after the initial 10 minutes of reperfusion, no visual changes could be observed, but a difference was noted within 30 to 60 minutes and usually correlated with the increment of the dP/dt_{max}.

I would like to mention that we have performed a small randomized blind study in patients undergoing myocardial revascularization on cardiopulmonary bypass. Coded medication was administered at the time of release of the aortic cross-clamp and then at intervals following the hemodynamic, inotropic, and diuretic requirements during the first 24 hours. The results of this study show that the T_3-treated patients required significantly less inotropes and diuretics than the placebo group. This was a small study, and the patients were probably undertreated as the plasma free T_3 levels showed no significant difference by 24 hours.

DR SIDNEY LEVITSKY (Boston, MA): I am trying to understand the mechanism of action of T_3 in these experiments. It is well known that T_3 increases myocardial oxygen consumption, which would make this drug particularly dangerous in patients with ischemic coronary artery disease, even after revascularization.

Second, you mentioned that you thought this drug had a true inotropic effect because dP/dt$_{max}$ increased. But as Dr Webb previously pointed out, without control of systemic vascular resistance, dP/dt$_{max}$ alone is a poor predictor of contractility.

Finally, I am concerned about the possibility of tachyphylaxis after the use of T_3; my question is, did you construct any dose-response curves?

DR NOVITZKY: It is accepted that T_3 stimulates aerobic metabolism. We do not know the exact mechanisms, as it is believed that the mitochondria do not have T_3 receptors that we know of and minimal to no effects are observed when isolated mitochondria are studied in vitro and T_3 is added. However, in vivo, there is a rapid increment of oxidative pathways.

It is known that in myocardial ischemia, the metabolic rate increases in the nonischemic area during the hyperdynamic phase, trying to compensate for the lack of function of the area at risk. Although the heart can extract oxygen at later stages, the mitochondria may become uncoupled, affecting ATP production.

The normalization of metabolic pathways results in more efficient utilization of oxygen. In presently ongoing experiments we have found that, after T_3 therapy, the stunned myocardium is again able to extract lactate from the coronary blood supply, improving the metabolic efficiency via aerobic pathways. I would like to hypothesize that T_3 is one of the major anabolic substances controlling ATP production and utilization.

Control of the afterload and preload in a whole animal, as in this model, is extremely difficult. In studies we have been performing in isolated hearts from pigs in a modified ex vivo working model (fix, preload, and afterload), we have shown that hearts from brain-dead animals pretreated with T_3 had significantly higher dP/dt than hearts from untreated animals.

Regarding the development of tachyphylaxis, we have not observed this phenomenon, as with conventional β-agonists. Rather we found that the combination of T_3 with β-agonists has synergistic effects. We have treated patients with T_3 who underwent cardiac operations and, as a result of left ventricular failure, were cardiopulmonary bypass–dependent. All of these patients received large doses of inotropes. After administration of T_3, within 1 hour we managed to discontinue cardiopulmonary bypass support and begin progressively reducing the inotropic requirement. I think the mechanism of action of T_3 is totally different from conventional inotropes, and we have not observed the phenomenon of tachyphylaxis in patients to whom I have administered this hormone over a period of 24 hours.

DR RICHARD D. WEISEL (Toronto, Ont, Canada): We have done similar experiments in dogs with 15 minutes of LAD occlusion followed by 6 hours of observation, and we found that cardiac output is normal during our observation period. We found that the anterior wall was stunned and that the posterior wall was hyperdynamic resulting in normal global function. Therefore, I was surprised to see that you found a decrease in cardiac output in your control group. Inotropic stimulation with T_3 may restore global function by stimulating hyperdynamic contraction of the posterior wall. However, the posterior wall should have been able to restore global function without inotropic stimulation. If the anterior wall was ischemic, then inotropic stimulation during reperfusion may induce further necrosis of the anterior wall. Therefore, T_3 may be contraindicated in patients recovering from regional ischemia. In addition, T_3 may be contraindicated in donors who have evidence of ischemic dysfunction before organ donation because it may cause progressive cardiac ischemia and deterioration in function.

DR NOVITZKY: I understand from your question that you ligated the LAD. Did you induce myocardial infarction or did you release the ligature at 15 minutes?

DR WEISEL: We induced a temporary occlusion of the LAD for 15 minutes followed by normal reperfusion for 6 hours.

DR NOVITZKY: Did you measure the percentage of the left ventricular mass that was at risk during the coronary occlusion?

DR WEISEL: We occluded the LAD distal to the first diagonal producing a 33% area at risk and a 2% area of infarction within the area at risk.

DR NOVITZKY: Well, I think we have two different models. We have temporarily occluded the LAD proximal to the first diagonal, observing that the mean area at risk was 43%. However, if the obstruction is distal to the first diagonal branch, the range varies between 12% and 38% with a mean of 30%.

DR WEISEL: We produced our obstruction distal to the first diagonal, and you had an obstruction proximal to the first diagonal. Therefore, you had a larger area of dysfunction. This difference could explain the deterioration in cardiac output that you saw in your animal studies.

It is possible that you induced dysfunction of the posterior wall in your model. You were then able to resuscitate the posterior wall with the infusion of T_3.

DR NOVITZKY: Correct.

DR WEISEL: You have demonstrated an inotropic effect of T_3 on the posterior wall of the heart restoring hyperdynamic function of this region and restoring global function. Therefore, the effect of T_3 was on the normally perfused myocardial segment rather than the ischemic segment. Stimulation of an ischemic segment may produce greater ischemic injury.

DR NOVITZKY: We are presently measuring the regional function by implanting two different sets of sonomicrometers, one in the area at risk and the second in the normally perfused myocardium. We have observed that, following an initial dyskinetic motion of the area at risk, there is a recovery of the contractility of this area after T_3 therapy. A different phenomenon is observed in the control animals.

DR WEISEL: If you were able to recruit function in the stunned myocardium, you may have induced greater ischemic injury. Stimulating a segment of myocardium that has suffered an ischemic insult usually results in greater necrosis within the area at risk. You need to carefully study the metabolic and functional recovery of the anterior wall in your model, and I am sure that you will perform these studies in the future.

DR NOVITZKY: I think you cannot make a conclusive statement that by recruiting the function of the stunned myocardium, it makes it worse metabolically. We have observed that there is a rapid functional recovery of the area that has been stunned, measuring arterial and venous lactate levels. We have found that the heart, rather than releasing lactate, starts actively extracting it from the coronary circulation, indicating that there is a functional and biochemical recovery. I would agree with you that this is an initial communication of an ongoing study, and as soon as we have more data available, they will be presented in future meetings.

Valve Replacement in Patients With Endocarditis and Cerebral Septic Emboli

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Cerebral septic emboli complicate the cases in 20% to 40% of patients with left-sided endocarditis but the management of these patients who require a valvar operation remains unclear. From 1980 to 1988, the incidence of cerebral septic embolus was 42% (n = 45) among 106 patients with endocarditis who underwent valve replacement at the University of Illinois Hospital in Chicago. Of these 45 patients, 69% (n = 31) had symptomatic cerebral septic infarctions and 31% (n = 14) were asymptomatic. Findings on cerebral computed tomographic scans included ischemic infarcts (n = 36, 80%), hemorrhagic infarcts (n = 5, 11%), normal studies (n = 2, 4%), and unknown (n = 2, 4%). Neurological complications after valve replacement included postoperative strokes (n = 6, 6%), cerebral abscesses (n = 2, 2%), and seizure (n = 1, 1%). The presence of a hemorrhagic infarct preoperatively predisposed to a perioperative stroke ($p < 0.05$). In conclusion, cerebral septic infarctions, both symptomatic and asymptomatic, are common among patients with endocarditis referred for valvar operation. In the absence of a hemorrhagic infarct, valve replacement can be performed with minimal risk of a perioperative stroke.

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The importance of cerebral septic infarctions in left-sided infective endocarditis is underscored by numerous series that have shown that the neurological complications of endocarditis were found in 20% to 40% of patients [1–3]. Of the neurological complications, cerebral septic embolization has been reported to be the most frequent and important [1, 2]. The concern of performing a valvar operation in patients with endocarditis complicated by cerebral septic infarcts is the potential conversion of an ischemic infarct to a hemorrhagic infarct with anticoagulation during cardiopulmonary bypass. Because the sample size of patients with surgically treated endocarditis is frequently small, it has been difficult to determine the rational management of these patients with combined endocarditis and cerebral septic infarcts who require a valvar operation. The large number of patients with endocarditis caused by both intravenous drug abuse and other causes who underwent valve replacement at the University of Illinois Hospital provided us with the opportunity to obtain a database on a number of pertinent variables including the preoperative evaluation, timing of valve replacement, risks of cardiopulmonary bypass, and natural history of cerebral septic infarctions. The overall objective of this retrospective study is to derive a strategy for the rational management of this subgroup of patients with endocarditis in order to reduce the risk of perioperative strokes and to avoid the worsening of existing neurological deficits.

For editorial comment, see page 6.

Material and Methods

Between January 1980 and December 1988, 106 consecutive patients who underwent valve replacement for left-sided infective endocarditis at the University of Illinois Hospital in Chicago were retrospectively analyzed by review of clinical records. Age at operation ranged from 18 months to 65 years with a mean age of 37 years. There were 77 male (73%) and 29 female patients (27%). Causes of surgically treated left-sided endocarditis included intravenous drug abuse in 74 patients (70%) and miscellaneous causes in 32 patients (30%). There were 46 aortic valve replacements (43%), 43 mitral valve replacements (41%), and 17 combined aortic and mitral valve replacements (16%). The causative microorganisms included streptococcus in 34 patients (32%), gram-negative bacillus in 29 patients (27%), staphylococcus in 22 patients (21%), culture-negative in 13 patients (12%), and miscellaneous microorganisms in 8 patients (8%).

Statistical analysis of data was by comparison of population proportions using χ^2. A p value of less than 0.05 was considered significant.

Results

There were 45 patients (42%) with cerebral septic embolus among the 106 patients with left-sided infective endocarditis who required valve replacement. Diagnosis of cerebral septic embolus was confirmed by cerebral computed tomographic (CT) scan. In this study group of 45 patients, age at operation ranged from 22 years to 61 years with a mean age of 40 years. There were 36 men (80%) and

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9 women (20%). Causes of infective endocarditis included intravenous drug abuse in 29 patients (64%) and miscellaneous causes in 16 patients (36%). There were 21 aortic valve replacements (47%), 15 mitral valve replacements (33%), and 9 combined aortic and mitral valve replacements (20%). The causative microorganisms included streptococcus in 16 patients (36%), staphylococcus in 13 patients (29%), gram-negative bacillus in 10 patients (22%), culture-negative in 4 patients (9%), and miscellaneous microorganisms in 2 patients (4%).

Of the 45 patients with cerebral septic embolus, 31 patients (69%) were symptomatic with neurological deficits and 14 patients (31%) were asymptomatic. Neurological findings included lateralizing deficits in 20 patients (44%), mental status change alone in 6 patients (13%), seizure alone in 2 patients (4%), and miscellaneous neurological deficits in 3 patients (7%).

Among the 106 patients, screening for cerebral septic infarction with CT scan was obtained preoperatively in 62 symptomatic and asymptomatic patients (58%). Thirty of 31 patients with symptomatic cerebral infarction before valve replacement were evaluated with preoperative cerebral CT scan. Screening CT scan was not performed routinely in all asymptomatic patients; only 32 CT scans (43%) were performed preoperatively in the 75 asymptomatic patients. Findings of cerebral CT scan among the 45 patients with cerebral septic infarction included ischemic infarcts in 36 patients (80%), hemorrhagic infarcts in 5 patients (11%), normal studies in 2 patients (4%), and unknown in 2 patients (4%). Cerebral infarctions were single in 26 patients (63%) and multiple in 15 patients (37%). The sizes of the cerebral infarctions were 2 cm or less in 33 patients (80%) and greater than 2 cm in 8 patients (20%).

Time interval to valve replacement from onset of neurological deficits in symptomatic patients or performance of CT scan in asymptomatic patients ranged from 1 to 49 days with a mean interval of 11.4 days.

Neurological complications among all 106 patients who underwent valve replacement included postoperative stroke in 6 patients (6%), cerebral abscess in 2 patients (2%), and seizure in 1 patient (1%). Among 31 patients with symptomatic cerebral infarctions preoperatively, 6 patients (19%) died perioperatively. Condition at discharge when compared with findings on admission of 25 surviving patients included worsening of neurological deficits in 3 patients (12%), unchanged neurological deficits in 4 patients (16%), partial resolution of neurological deficits in 5 patients (20%), and complete resolution of neurological deficits in 13 patients (52%). Among the 14 patients with asymptomatic cerebral septic infarctions, 1 patient (7%) died in the postoperative period. The other 13 patients remained free of symptoms at discharge. None had a perioperative stroke. Hospital mortality among the 106 patients was 10 patients (9%); among the 45 patients with cerebral septic infarctions, 7 patients (16%); among the 31 patients with symptomatic cerebral septic infarctions, 6 patients (19%); and among the 14 patients with asymptomatic cerebral septic infarctions, 1 patient (7%).

Statistical analysis of the patient population with endocarditis and cerebral septic emboli revealed no significant difference ($p > 0.05$) in age at operation, sex, causes of endocarditis, locations of involved valves, and causative microorganisms when compared with overall patient population with surgically treated left-sided infective endocarditis. The only risk factor that correlated ($p < 0.05$) with perioperative strokes was the finding of a hemorrhagic infarct on the preoperative CT scan. Timing of valve replacement, finding of an ischemic infarct alone, size of cerebral septic infarction, and multiple cerebral infarctions were not significant risk factors ($p > 0.05$). Operative mortality was significantly increased in the presence of a preoperative hemorrhagic infarct ($p < 0.05$) but not with an ischemic infarct ($p > 0.05$).

Comment

The prevalence of neurological complications in endocarditis was alluded to in 1855 by Osler [4] when he described the triad of fever, heart murmur, and cerebral "trouble" associated with endocarditis. More recent studies have continued to demonstrate a high incidence of neurological complications ranging from 20% to 40% of patients with infective endocarditis [1–3]. The incidence of cerebral septic embolization in our series of 106 patients with left-sided infective endocarditis requiring valve replacement was 45 patients (42%). This incidence is higher than the incidence reported in most other series [1–3]. The difference in reported incidence may be due to our patient population, which consisted of only surgically treated infective endocarditis, whereas most other series were made up of patients with endocarditis during medical therapy [1, 2]. It is probable that patients with endocarditis who failed pharmacologic therapy and required surgical intervention have a higher incidence of cerebral septic embolization due to more advanced infection, more virulent microorganisms, and longer time during medical therapy for septic embolization to occur.

Although other studies have shown that cerebral emboli were associated with endocarditis of the mitral valve and with virulent organisms, particularly *Staphylococcus aureus*, enterococci, and *Escherichia coli* [2], our series of patients with surgically treated endocarditis showed an incidence of cerebral septic infarction that did not vary significantly among patients by age, sex, cause of endocarditis, causative microorganism, or type of left-sided valve involved. Contrary to published reports, our findings showed that all patients with endocarditis referred for valvar operation are equally at risk for cerebral septic infarctions.

The rational management of patients with combined endocarditis and cerebral septic infarction who require a valvar operation is predicated on the accurate diagnosis of cerebral septic infarction. The value of physical examination alone in screening patients for cerebral septic infarction is limited by the substantial number of asymptomatic patients. We have shown that cerebral septic infarcts were not always symptomatic. Therefore, using the presence of symptoms alone as a basis to initiate further evaluation will miss many patients with cerebral septic infarctions who are asymptomatic. Among our 45 patients with confirmed cerebral septic infarctions, 14 patients (32%) were asymptomatic. In addition, 43 asymptomatic patients in the series did not undergo any neurological evaluation beyond the routine history and examination on admission. It is likely that at least some of these patients might have had asymptomatic cerebral septic infarctions identified with additional investigation. The prevalence of symptomatic and asymptomatic cerebral septic infarctions in all patients with left-sided infective endocarditis requiring surgical intervention underscores the importance of a thorough neurological evaluation in all such patients before operation unless precluded by a need for emergency valve replacement.

We have found that cerebral CT scan is by far the most effective and convenient tool for the initial diagnosis and subsequent monitoring of cerebral septic infarctions. Among the 45 patients in our series with cerebral septic emboli, it accurately revealed the location and size of the infarcts as well as, whenever present, intracerebral blood, cerebral edema, and midline shift. Cerebral ischemic infarcts appear as low-density areas, which have been reported by others to be visible in 5% of cases in the first 4 hours, 50% by the first day, and 95% by the eighth day [5, 6] (Fig 1). Cerebral CT scan can readily detect infarcts of 1 cm in diameter, but smaller infarcts less than 5 mm are difficult to detect [5, 6]. In contrast, hemorrhagic infarcts appear as high-density areas on the cerebral CT scan, which can detect the presence of intracerebral blood with excellent accuracy [6] (Fig 2).

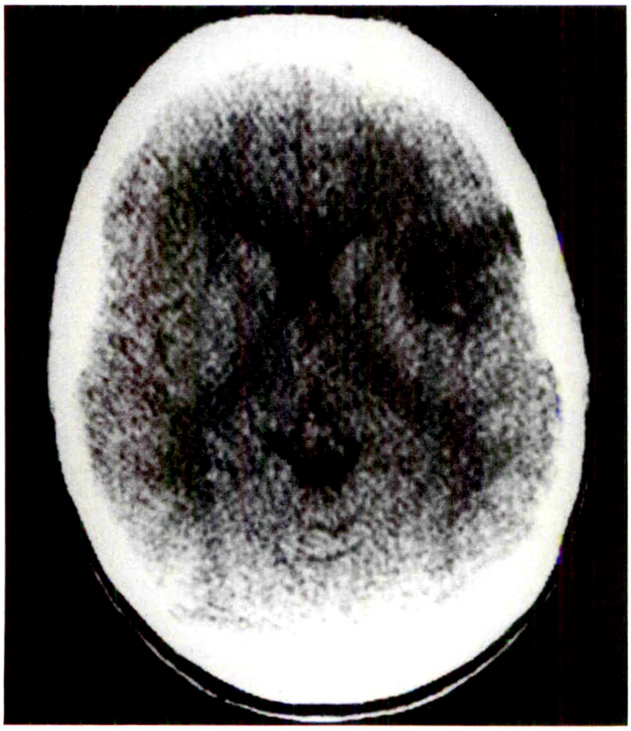

Fig 1. Noncontrast computed tomographic scan showing a low-density area suggestive of an ischemic infarct in the left frontal lobe from a cerebral septic embolus.

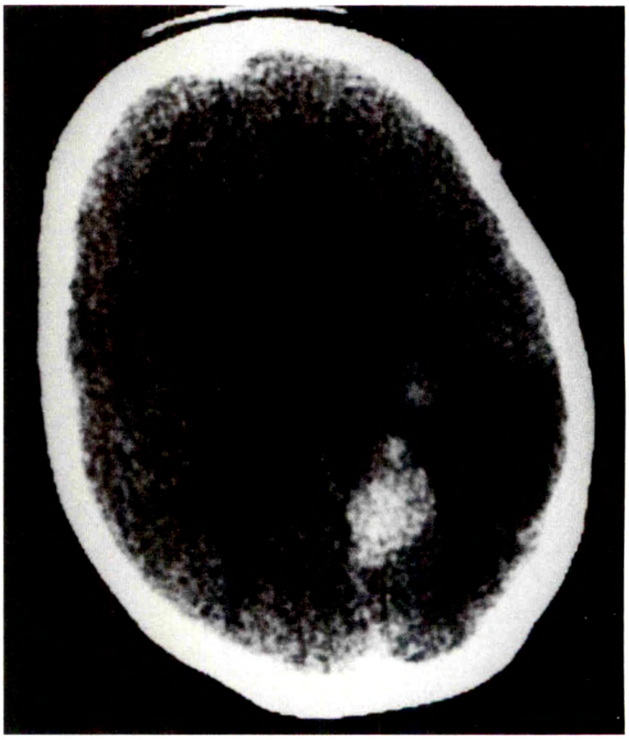

Fig 2. Noncontrast computed tomographic scan showing a high-density area suggestive of a hemorrhagic infarct in the left parietal-occipital region from a cerebral septic embolus.

Although not used by us, others have reported experience with alternative diagnostic modalities such as magnetic resonance scanning, which may be superior to CT scanning in the diagnosis of cerebral septic infarctions [4, 7, 8]. The advantages of magnetic resonance scans include better resolution, earlier visualization of infarcts, and avoidance of intravenous contrast materials; however, current access to magnetic resonance scans remains limited [7, 8]. Lumbar puncture may be helpful if CT scanning is not available for the diagnosis of intracerebral blood but its use is limited because it has been shown by others that 20% to 50% of patients with confirmed intracerebral hemorrhage have no evidence of blood in their cerebral spinal fluid [9]. The use of angiography also has been reported, which will show an avascular area with vessel displacement in a cerebral infarction and usually vessel displacement alone in a cerebral hemorrhage [10]. Angiography is limited by a higher complication rate, need for intravenous contrast medium, and the greater technical demand of the procedure [11]. Currently, the role of cerebral angiography in endocarditis is limited to the diagnosis of suspected mycotic aneurysms [12]. Radioisotope scanning has largely been replaced by CT scanning because it is less sensitive, is less specific, gives no information on midline shift, and does not differentiate between ischemic and hemorrhagic infarcts [13].

The primary concern in the management of a patient with combined endocarditis and cerebral septic infarction who requires a valvar operation is the risk of a perioperative stroke. The decision to operate depends on the balance of the risk of cerebral hemorrhagic complication against the risk of further embolization or cardiac decompensation. Among the 45 patients with cerebral septic infarcts in our series, 6 patients (13%) had a perioperative stroke. Preoperative CT scan demonstrated intracerebral blood in 5 of the 6 patients and 1 patient did not undergo preoperative CT scanning owing to the urgent basis of his valve replacement. None of 36 patients with preoperative ischemic infarctions on CT scan and none of 43 asymptomatic who were not studied with CT scan sustained a perioperative stroke. The data suggest strongly that the major risk factor associated with perioperative strokes is the presence of a hemorrhagic infarct preoperatively. There was no clinical evidence in our study that anticoagulation in ischemic strokes had converted a pale infarct into a hemorrhagic infarct.

The timing of valve replacement in patients with endocarditis and cerebral septic infarcts is dependent on whether the infarct is ischemic or hemorrhagic. For patients with ischemic infarcts, the timing of valvar operation did not appear to have a significant effect on the outcome. The inference of our findings must be tempered with the limitations of our study, in which most of the ischemic infarcts were small, measuring 1 to 2 cm in diameter. Although not reflected in our data, it is reasonable to include the clinical condition of these patients with an ischemic infarction alone in the decision concerning operation. If the patient is hemiplegic or has a decreased level of consciousness, it can be assumed that a large area of cerebral tissue has infarcted. In this situation, one may well wait several days before proceeding with valve replacement if the risks of cardiac decompensation and further embolic complications are not excessively high. For patients with hemorrhagic infarcts, early valvar operation had been associated with significant risk of a perioperative stroke and death. For these patients with hemorrhagic infarcts, the benefits of a valve operation should be balanced against the nearly universal poor outcome. If one is compelled to operate on these patients, one probably should delay operation until there is stabilization or improvement of neurological deficits, confirmation that mental status change is not permanent, and absence of roentgenographic evidence of ongoing infarct expansion.

The natural history of patients with endocarditis and cerebral septic emboli after valvar operations varied according to characteristics of the resultant cerebral infarctions. Among the asymptomatic patients, the risks of operation were not significantly different from patients without cerebral septic embolus and the postoperative course remained free from any neurological sequelae. The patients with symptomatic cerebral septic emboli and resultant hemorrhagic infarcts were at significantly higher risks for perioperative strokes, death, and irreversible or worse neurological deficits. Many patients with symptomatic ischemic infarcts had partial or complete resolution of their neurological deficits, especially if the cerebral infarcts were less than 2 cm in diameter.

In summary, our experience with surgically treated left-sided infective endocarditis pointed to a high incidence of cerebral septic embolization preoperatively among these patients. Neurological evaluation should be obtained in all patients regardless of symptoms before valve replacement whenever feasible. The CT scan is a reliable study for the identification of cerebral septic infarction and for the differentiation between ischemic and hemorrhagic infarct. In the absence of intracerebral hemorrhage, valve replacement can be performed with a minimal risk of perioperative stroke. The natural history of ischemic infarcts, especially when less than 1 to 2 cm in diameter, is frequently one of complete recovery.

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DISCUSSION

DR ADNAN COBANOGLU (Portland, OR): I would like to congratulate Dr Ting and his associates for a potentially very important and informative review of their experience with valve replacement in patients with endocarditis and cerebral septic emboli.

Neurologic complications have been recognized as some of the most life-threatening complications of infective endocarditis since Osler first described the triad of fever, heart murmur, and hemiplegia in 1855. The reported incidence of this phenomena has ranged from 9% to 80% with an average of about 25% being a reasonable overall estimate.

Today more effective antimicrobial therapy has markedly diminished the number of patients dying of uncontrolled sepsis with infective endocarditis, and more effective treatment of congestive heart failure has reduced early deaths from hemodynamic causes. As a result, an increasing number of patients with virulent organisms infecting their heart valves now survive long enough for cerebral emboli to develop.

This report by Dr Ting and associates is important in that it shows that cerebral septic infarcts were not always symptomatic and that using symptoms alone would miss many patients with cerebral septic infarctions who were asymptomatic. Among their most important findings is that, of the 45 patients with cerebral septic infarcts, 6 patients (14%) had a perioperative stroke. Preoperative CT scan demonstrated intracerebral blood in 5 of these 6 patients. I agree with their conclusion that patients with infective endocarditis have a high incidence of cerebral emboli and in such a patient, even simple altered level of consciousness should promote a CT scan. A detailed neurological evaluation should be performed in every patient.

I have a few questions for the authors. It was not clear as to how many patients exactly had frank strokes preoperatively. Also, could you speculate about the discrepancies that your report has compared with other reports in the literature? For example, the most common causative agent in such a patient is usually staphylococcus. It is reported to be as high as 70% in these type of cases, although in your series it is only 29%.

In nearly all reports, septic cerebral emboli have occurred mostly in patients with infective endocarditis affecting the mitral valve. Why is this different in your series?

What was the relationship and duration of antibiotic therapy with regard to operation?

Could some of the hemorrhagic infarcts been due to myocotic aneurysms rather than septic emboli?

Finally, how accurate is CT scan in differentiating between an embolic infarct and an embolic abscess? This is important because these conditions have different surgical implications.

I congratulate Ting and associates again. I think this paper is an important contribution.

DR TING: Of the 45 patients with cerebral septic emboli, 68% were symptomatic, most of whom had lateralizing neurological deficits. Many of these strokes were minor; the neurological deficits were frequently improved before valvar operation.

The discrepancies such as the causative agents in endocarditis between our study population and others reflected the demographic composition of our patients.

Other reports have shown that cerebral septic emboli occurred mostly in patients with infective endocarditis affecting the mitral valve. This difference may be explained by differences in timing of valvar operation between aortic and mitral valve endocarditis. I wonder whether patients with endocarditis of the aortic valve are referred earlier for operation and therefore have a shorter time interval for embolic events to occur.

Most of these patients have undergone at least 1 to 2 weeks of antibiotic therapy before their valve replacement. Many patients have been on antibiotic therapy for as long as 4 to 6 weeks preoperatively.

Rupture of a mycotic aneurysm causes a clinical picture similar to a hemorrhagic infarct. Therefore some of the hemorrhagic infarcts could have been due to mycotic aneurysms, but this is unlikely because septic embolization to vessel walls appeared rare in infective endocarditis.

The CT scan is very accurate in differentiating between an embolic infarct and an embolic abscess. It is currently the most convenient tool for the screening of patients with endocarditis and possible cerebral septic emboli.

Tracheoesophageal Anastomosis for Intractable Aspiration Pneumonia

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Permanent tracheostomy and tracheoesophageal anastomosis were performed as a means of surgical intervention for the treatment of intractable aspiration pneumonia. Conventional methods of tracheoesophageal anastomosis have entailed various problems. The improved method devised by us uses the special histological features and enables safe and reliable anastomosis. By this method, the tracheal perichondrium is retained and the strength of the anastomosed portion of the trachea is maintained, the failure of sutures due to tension on the anastomotic site being prevented. Also, reanastomosis can be performed after the cure of primary disease.

(Ann Thorac Surg 1991;51:23–9)

Faulty deglutition is the most serious problem for patients with depression or loss of normal neurological function of the glottis. The causes of impairment of normal glottic function are diverse and extremely complex. Moreover, there exists no therapeutic method definitely effective against such disorders, and the treatment of various concomitant symptoms such as dysphagia and aspiration of food has generally consisted of tracheotomy and suction of the airway. Also, the method of inserting a tracheal cannula fitted with a balloon cuff has been tried to secure the airway and prevent aspiration of food, but as this method is still inadequate and merely palliative, the radical therapeutic method has been a vital desideratum. To this end, a number of surgical techniques are currently being selected and applied in accordance with the nature of the underlying disease. We have applied tracheoesophageal anastomosis to cases of intractable aspiration pneumonia concomitant with amyotrophic lateral sclerosis. This is a highly effective method and, owing to the addition of certain improvements over the existing technique, provided excellent results, which are here reported in greater detail.

Material and Methods

Case Reports

PATIENT 1. The first patient was a 64-year-old man. Dysarthria and dysphagia appeared about May 1986, and reduced muscular power in the distal portions of all four limbs became evident. Examination revealed systemically distributed fasciculation and bilateral hyperactivity of the pharyngeal reflex as well as atrophy, fasciculation, and deep hyperreflexia of the tongue. The condition was diagnosed as amyotrophic lateral sclerosis. Tracheostomy was carried out immediately, and when the condition was improved, the patient was discharged even though in need of nocturnal assisted respiration. However, at the end of December 1986, aspiration pneumonia recurred, and the patient was readmitted to the hospital. Treatment of this pneumonia was extremely difficult, and mechanical ventilation was necessary. As oral feeding was impossible, tube feeding was started. Resistant *Pseudomonas pyocuanea* strains were isolated from the sputum. In April 1987, this case of intractable aspiration pneumonia was surgically treated by tracheoesophageal anastomosis and permanent tracheostomy. Seven days after operation, pneumonic symptoms rapidly improved, and the patient was discharged. Home treatment is now possible.

PATIENT 2. The weight of a 46-year-old man decreased by approximately 10 kg in a period of 6 months from about January 1985. Dysphagia and respiratory difficulty during work appeared about September. Bilateral hyperactivity of the deep reflexes and appearance of Babinski and Chaddock reflexes were detected as well as symptoms of bulbar palsy. On the basis of electromyograms and muscular biopsies, the condition was diagnosed as amyotrophic lateral sclerosis. Aspiration pneumonia came to occur frequently, and therefore tracheostomy was performed. Pneumonia was rapidly ameliorated by intratracheal suction, but pneumonia again became frequent about December 1986. Also, deglutition of food became difficult, and hence the patient's oral intake of nutrients was markedly reduced. Consequently, tracheoesophageal anastomosis, permanent tracheostomy, and gastrostomy were performed in February 1987. Postoperative progress was satisfactory, and the symptoms of aspiration pneumonia rapidly disappeared.

PATIENT 3. The third patient was a woman, 68 years of age. About October 1985, muscular weakness in the distal portions of all four limbs became evident. The patient displayed progressive dysarthria and dysphagia, likely to

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Table 1. Characteristics of Patients With Tracheoesophageal Anastomosis

Patient No.	Age (y)	Sex	Diagnosis	Precautionary Treatment	Radical Treatment	Result	Follow-up (y)[a]
1	64	M	ALS	Tracheostomy, NG tube feeding for 6 mo	TE anastomosis, gastrostomy	Died of respirator trouble	4.5
2	46	M	ALS	Controlled ventilation for 3 mo	TE anastomosis, gastrostomy	Alive	3.6
3	68	F	ALS	Controlled ventilation for 1 mo	TE anastomosis, gastrostomy	Alive	3.5
4	56	M	CVA	Controlled ventilation, tracheostomy, NG tube feeding for 1 mo	TE anastomosis, gastrostomy	Alive	3.3
5	47	M	ALS	NG tube feeding for 6 mo	TE anastomosis, gastrostomy	Alive	2.2
6	45	M	ALS	Tracheostomy for 1 mo	TE anastomosis, gastrostomy	Alive	2.0
7	43	M	ALS	NG tube feeding for 10 mo	TE anastomosis	Alive	1.6
8	52	M	ALS	Tracheostomy for 8 mo	TE anastomosis	Alive	1.4

[a] Length of follow-up after TE anastomosis.

ALS = amyotrophic lateral sclerosis; CVA = cerebrovascular accident; NG = nasogastric; TE = tracheoesophageal.

result from bulbar palsy, and the condition was diagnosed as amyotrophic lateral sclerosis. From about January 1987, recurrent episodes of pyrexia at 39°C emerged, and the patient was hospitalized with a diagnosis of aspiration pneumonia. However, the pneumonic syndromes were aggravated, and no signs of improvement were observed. Therefore, in January 1987, tracheoesophageal anastomosis and permanent gastrostomy were performed. Thereafter, the pneumonic syndromes had rapid improvement, and home treatment became possible. Though controlled ventilation was needed, the patient was discharged.

PATIENT 4. In October 1986, a 56-year-old man suffered cervical vertebral fracture and head contusion by traffic accident. His consciousness level gradually declined. The patient was diagnosed by computed tomographic scanning to have an intracranial hematoma. The hematoma was removed by operation, but the patient did not recover consciousness. Moreover, aspiration pneumonia recurred frequently, and the artificial respirator was needed throughout the day. Therefore, tracheostomy was carried out. Subsequently, improvement of pneumonia was noticed, and though controlled ventilation was still needed, the patient was discharged. At the end of April 1987, pneumonia recurred, and the patient was readmitted to the hospital. Intractable aspiration pneumonia was surgically treated by tracheoesophageal anastomosis and permanent tracheostomy. After operation, pneumonic symptoms improved rapidly. Home treatment is now possible.

PATIENT 5. A 47-year-old man had dysphagia and dysarthria about September 1987. The patient was admitted to the hospital for tests, which revealed bilateral hyperactivity of the pharyngeal reflex as well as atrophy. The condition was diagnosed as amyotrophic lateral sclerosis. Aspiration pneumonia came to occur frequently, and therefore, tracheoesophageal anastomosis, gastrostomy, and permanent tracheostomy were performed. Postoperative progress was satisfactory, and the symptoms of aspiration pneumonia rapidly disappeared.

PATIENT 6. Patient 6 was a 45-year-old man. About July 1988, muscle weakness in the distal portions of all four limbs became evident. The patient was admitted to the hospital for tests, which revealed systemically distri-buted fasciculation and bilateral hyperactivity of the pharyngeal reflex as well as atrophy. On the basis of electromyogram and muscular biopsy, the condition was diagnosed as amyotrophic lateral sclerosis. Aspiration pneumonia came to occur frequently, and therefore, tracheoesophageal anastomosis and permanent tracheostomy were performed. Postoperative progress was satisfactory, and the symptoms of aspiration pneumonia rapidly disappeared.

PATIENTS 7 AND 8. We had another 2 patients who were diagnosed as having amyotrophic lateral sclerosis and underwent tracheoesophageal anastomosis. They are presented in Table 1.

Surgical Technique

Under general anesthesia, the patient undergoes tracheostomy. A horizontal skin incision is made at the site of the existing tracheostomy or at the level of the second tracheal ring and carried down to the level of the trachea. The peritracheal adventitial tissues are carefully dissected

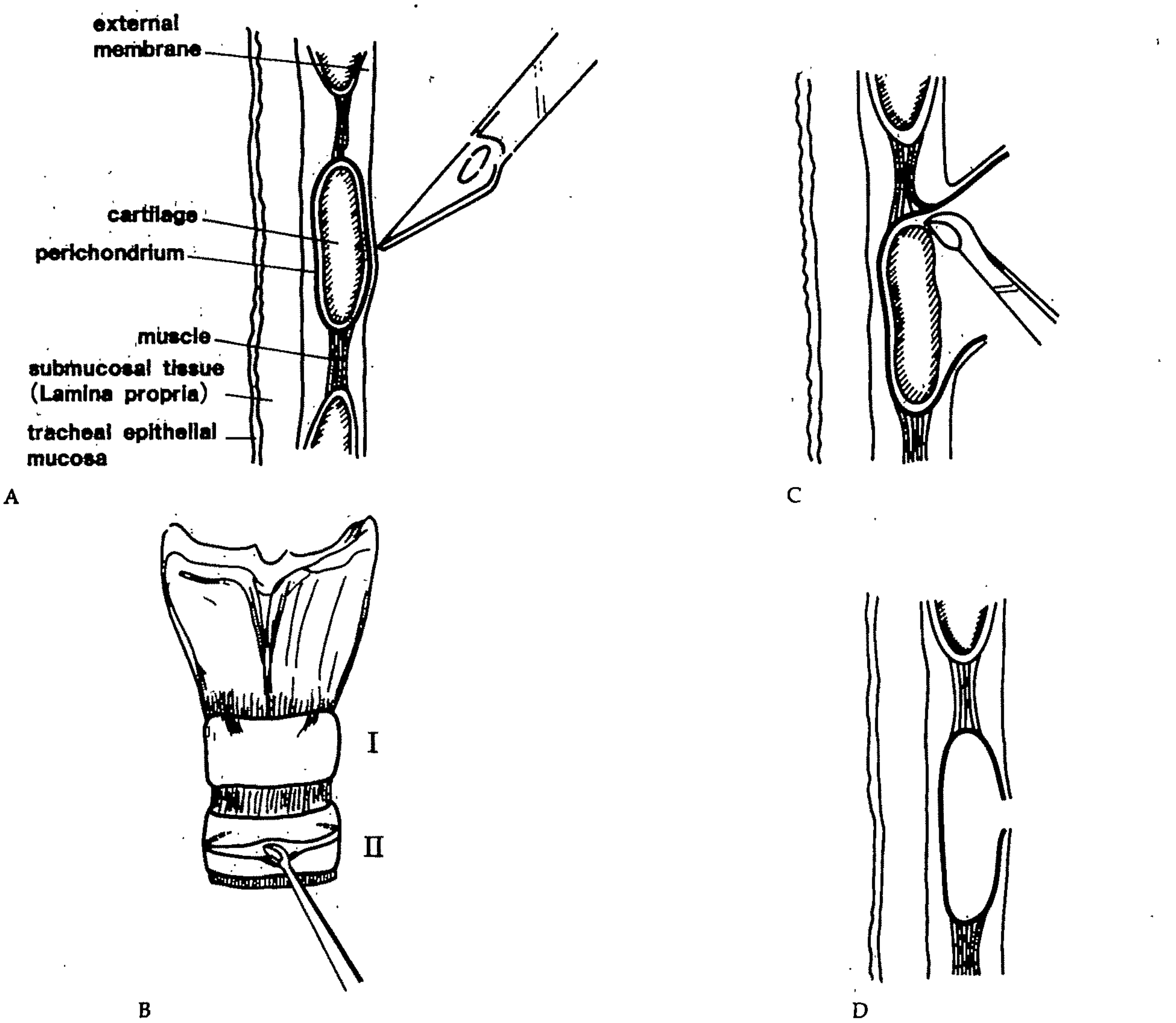
external membrane
cartilage
perichondrium
muscle
submucosal tissue (Lamina propria)
tracheal epithelial mucosa
A
C
I
II
B
D

Fig 1. (A) Incision of outer membrane and perichondrium. (B) Detachment of outer membrane and perichondrium. (C) The cartilage is detached with a surgical spoon. (D) Tissue is strengthened by retaining double layer of perichondrium.

away from the cricoid and the first and second tracheal rings. The incision should be made along the full length of the cartilage, penetrating to the external membrane and perichondrium. Then, with the external membrane and perichondrium carefully kept together, the cartilage is detached with a surgical spoon. Separation of the anterior surface of the cartilage is simple. In this process, it is vital to avoid damaging the tracheal mucosa. The detachment is performed completely up to the membranous portion of the trachea, so that no cartilage remains (Fig 1).

Concerning the detachment of the esophagus from the trachea, because bronchial capillaries of the trachea penetrate the membranous portion and submucosal region, blunt separation must be performed with great care (Fig 2). Tension on the site of tracheoesophageal anastomosis can be reduced by sufficient detachment and release of the esophagus from the posterior mediastinum. If tracheostomy has previously been performed, then the trachea is transected at the site of the previous operation. However, if all these operations are performed at once, then the trachea is transected between the second and third tracheal cartilages.

Esophagotomy is performed at the level of the resected portion of the trachea (Fig 3A).

Layer-to-layer suture is desirable for the tracheoesophageal anastomosis. The submucosa of the trachea is sutured to the esophageal submucosa, and the perichondrium and external membrane of the trachea are sutured to the tunica muscularis esophagi (Fig 3B).

The inner suture material used is absorbable thread (polyglycolic acid), and continuous suture is desirable. Suturing of the outer membrane is best performed by knot suture using silk thread (Fig 4).

The tunica muscularis esophagi is sutured to the outer membrane in such a manner as to envelope the trachea. It is not necessary to provide a drain for the anastomosis.

The distal stump of the trachea is withdrawn through a cutaneous incision at the superior margin of the sternum to form the permanent tracheostoma.

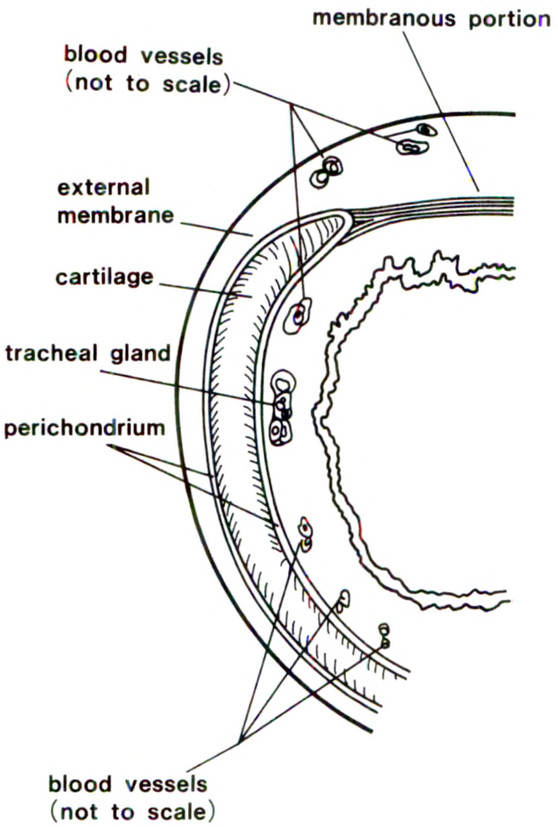

Fig 2. An incision is made in the adventitia and perichondrium at the center of the cartilage, and with due care, the perichondrium is bluntly separated. The vasculature of the trachea is principally controlled by the arterioles that penetrate the membranous portion and submucosal regions of the trachea. It is vital to avoid damaging these vessels.

Results

This procedure was performed successfully in 8 patients. The diagnosis of the 7 patients with amyotrophic lateral sclerosis was made on a neurological basis.

Intractable aspiration was relieved in all. Reversion is theoretically possible with this procedure but has not been performed, as the underlying neurological conditions have not improved. One patient (patient 1), who had been suffering from amyotrophic lateral sclerosis, died of respirator trouble. The macroscopic findings of the anastomosis site are shown in Figure 5. The anastomosis was done perfectly.

After operation, radiographic transesophageal imaging shows no movement of the epiglottis whatsoever and also reveals the influx of contrast medium into the esophagus through the anastomotic site (Fig 6).

Comment

In patients with progressive irreversible diseases such as amyotrophic lateral sclerosis, faulty deglutition induced along with the appearance of symptoms of respiratory distress causes aspiration pneumonia and finally leads to death. There exists no type of radical therapy for this lethal aspiration pneumonia other than surgical intervention with the purpose of achieving complete separation of the respiratory system from the digestive one. In recent years, tracheostomy has tended to become a semiemergency method for the long-term management of patients with severe respiratory insufficiency, and not merely an emergency measure for the maintenance of an air pathway. However, Cameron and associates [1] reported that faulty deglutition was observed in approximately 70% of patients who had undergone tracheostomy. Faulty deglutition occurred frequently also in tracheostomized pa-

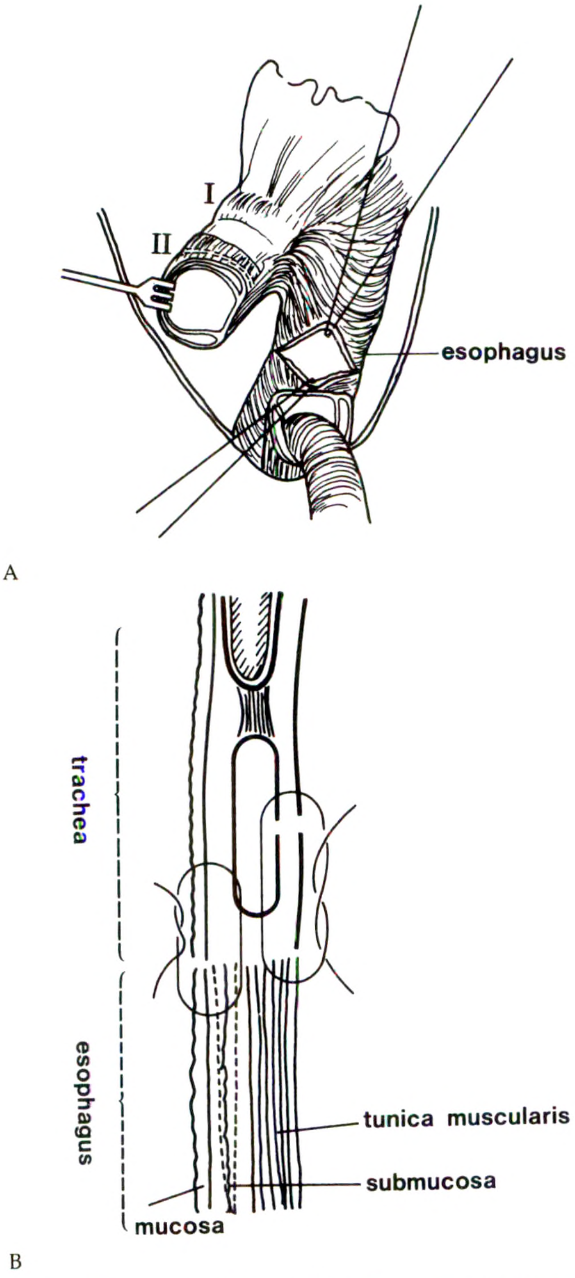

Fig 3. (A) The trachea is dissected between the second and third tracheal rings. The esophagus is traversely incised at this level and anastomosed with the trachea. (B) The suture is made layer to layer with polyglycolic acid thread.

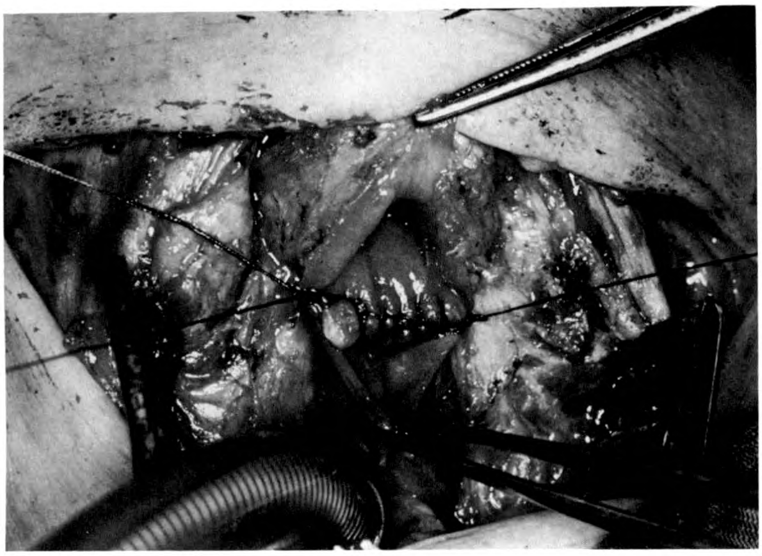

Fig 4. In tracheoesophageal anastomosis, continuous suture is applied to the inner side, and knot suture to the outer membrane.

tients even without glottic abnormalities [2]. It is readily supposed that the incidence of faulty deglutition and of consequent aspiration pneumonia in patients with amyotrophic lateral sclerosis who have symptoms of bulbar palsy is even higher [3, 4].

Various surgical modalities have been devised to deal with morbid changes arising from these types of progressive disorders, including (1) tracheostomy, (2) closure of the tracheal orifice, and (3) diversion of the cricopharyngeal muscle (cricopharyngomyotomy). As already mentioned, tracheostomy entails frequent tracheal suction, whenever aspiration of food occurs. Moreover, even when a tracheal cannula fitted with a balloon cuff is used, complete prevention of food aspiration is still impossible [4].

Closure of the tracheal orifice was tried by Habal and Murray about 1972 [5]. The arytenoid cartilage and epiglottis are sutured together and covered with a muscular valve. However, defects in suturing were prone to occur, and the surgical stress involved was great.

Subsequently, sutural occlusion of the vocal chords was reported by Montgomery [6]. However, the use of this method inevitably led to increasingly defective sutural closure with the lapse of time, and glottic stenoses were formed with high incidence. Sasaki and associates [7] improved on the method of Montgomery by using sutural occlusion of the vocal chords combined with a muscular valve; this was indeed an efficient method, but it involved the problem of digestion of the muscular valve and required a major structural alteration with laryngotomy and occlusion of the vocal chords that imposed a considerable surgical stress on patients.

Cricopharyngomyotomy represents an attempt to improve ingestion of food by resecting the cricopharyngeal muscle and thus relieving abnormal deglutition. The muscle is longitudinally incised and then divided to reduce the sphincter function, to diminish abnormal deglutitive movement of the laryngeal pharynx, and thus to facilitate the smooth passage of food toward the lumen of the esophagus [8]. Berg and colleagues [9] reported that this method was ineffective in 40% of the cases in which it was attempted. Cricopharyngomyotomy was not effective in all patients with deglutitive impediments, which suggested that careful consideration should be given in selection of cases suitable to this method [9, 10]. Also, Lebo and associates [11] indicated that this type of myotomy might be effective in cases where the deglutitive movement is existent, although improperly coordinated but not be appropriate for progressive disorders such as amyotrophic lateral sclerosis, in which the deglutitive movement is completely lost.

Thus, various reports indicate that the surgical techniques listed above are applicable only to a limited range of cases and moreover that, with progress in disease, the use of other methods is required.

Division and separation of the trachea from the larynx was performed by Lindeman in 1975 [12]; tracheoesophageal anastomosis and permanent tracheostomy were carried out. This is an excellent method for achieving the complete prevention of faulty deglutition. However, as Lindeman himself pointed out, a number of problems still remain [12]. The greatest of these problems is the difficulty in applying the technique to the cases in which tracheostomy has already been performed and the position of the stoma is comparatively high. The reason for this is said to lie in the technical difficulty of anastomosing the trachea to the esophagus in such cases [13]. Also, to separate the trachea from the larynx, Baron and Dedo [14] performed a transection of the trachea and did not anastomose the oral stump of the trachea to the esophagus, but merely created a cul-de-sac by closing the stump. This technique possesses the advantage of permitting occlusion even in cases in which the tracheostoma is located at a high position, eg, the first cartilage ring.

However, Krespi and associates [15] pointed out that the closure of the tracheal stump and the formation of a cul-de-sac below the glottis results in the constant stagnation of saliva and residue of improperly swallowed food

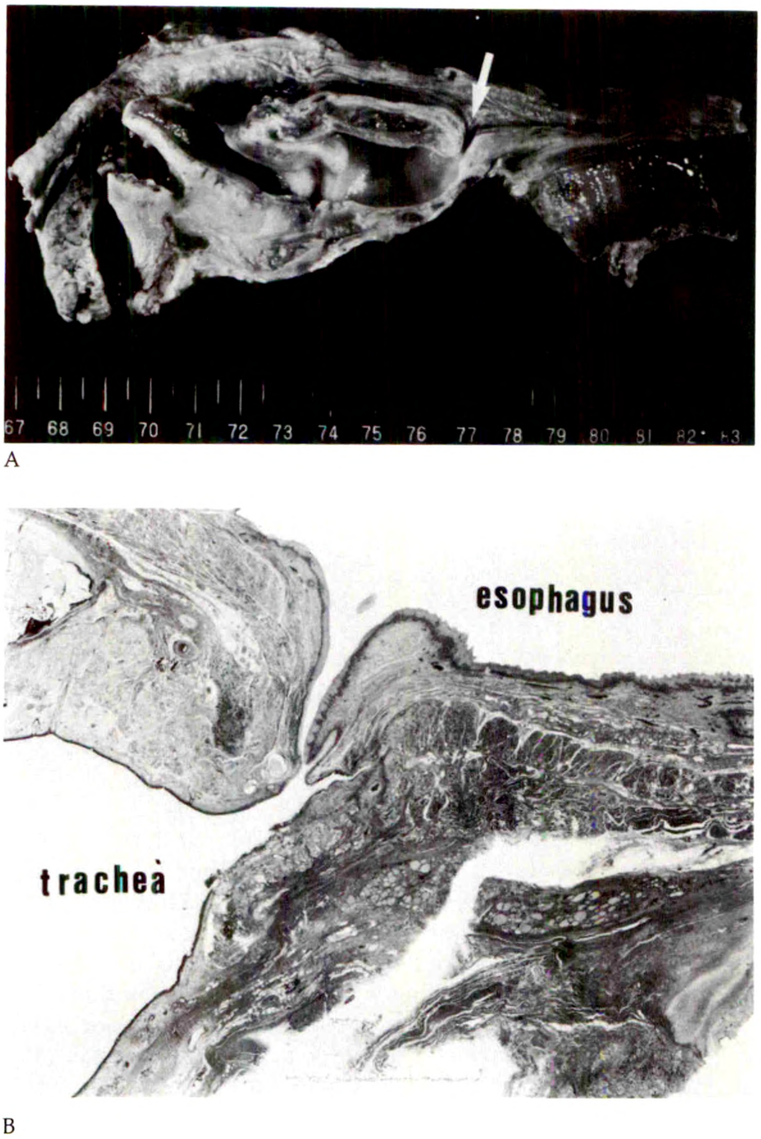

Fig 5. (Patient 1.) On longitudinal cut section of the esophagotracheostomy, squamous epithelium of the esophagus is continuous to the ciliated columnar epithelium of the trachea at the anastomotic site. The arrow *indicates the anastomotic site. (A) Macroscopic finding. (B) Microscopic finding.*

and hence does not necessarily constitute an ideal mode of surgery. They maintain that the cricoid cartilage should be resected and that the released tracheal mucosa should be anastomosed to the esophagus.

However, the method of Krespi and associates is also very difficult from a technical viewpoint. In elderly patients, the cricoid and first tracheal cartilages are ossified or fibrotic, so that the detachment from the mucosa is quite difficult.

Upon due consideration of these various methods, we decided that tracheoesophageal anastomosis would be the most appropriate method for the separation of the trachea from the larynx. Accordingly, we have added certain improvements to the method of Krespi and associates and devised a technique for preparing an anastomotic site at the oral end of the transected trachea in an easier and safer manner.

The exterior of the tracheal cartilages is completely covered with the perichondrium. Although the perichondrium is tough, the tissues interior to this comprise only the thin tracheal epithelium and the connective tissues (see Fig 1). By completely retaining the perichondrium, the method provides tissues strong enough to permit effective anastomosis, ie, one layer of perichondrium is sutured to the mucosal epithelium and submucosa, and another layer to the tunica muscularis (see Fig 3B).

This surgical technique was applied in 8 patients (see Table 1). In 4 of these patients, although tracheostomy had already been performed at the height of the first or second tracheal cartilage, secure end-to-side suture was easily accomplished. Even if the site of the stoma is as high as the first cartilage ring, tracheoesophageal anastomosis can be safely achieved by the present method. In the studies reported here, the method was applied only to 7 patients with amyotrophic lateral sclerosis and a patient with cerebral bone injury. One patient (patient 1) unfortunately died of respirator trouble, but another 7 patients tolerated this method well. Home treatments using a mechanical ventilator are now possible. Pneumonia, the cause of death for patients with amyotrophic lateral sclerosis, is controlled completely, and all of these patients are now healthy, with the longest survival period being 3.6 years. In cases in which recovery from the underlying disease makes the tracheostoma unnecessary, reanastomosis of the trachea and reclosing of the esophagus can be performed.

At present, endoscopic gastrostomy is usually applied to patients with amyotrophic lateral sclerosis, but the antireflux procedure is a little troublesome and is rarely performed. However, we believe that both of these operative methods should be applied to not-so-severe cases. In cases where amyotrophic lateral sclerosis is advanced and intractable aspiration occurs so frequently as to advance pneumonia to the lethal stage, tracheal diversion is a radical therapy.

In comparison with previous modes of operation, the present method entails little surgical stress on patients and is relatively safe. Moreover, the flow of saliva or food presents no subsequent problems. This method appears worthy of trial not only for patients with amyotrophic lateral sclerosis but also for various types of intractable cases requiring long-term respiratory management.

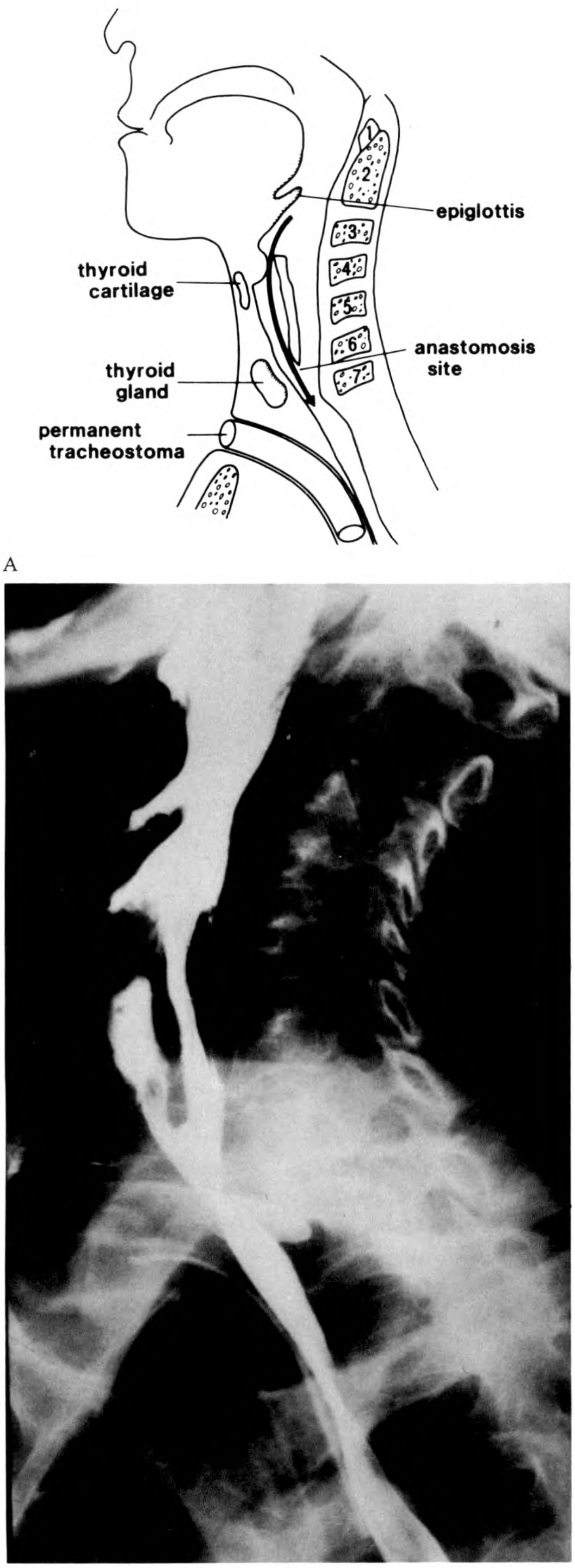

Fig 6. Radiographic transesophageal imaging shows that the contrast medium eventually flows into the esophagus through the esophagotracheostomy.

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Binding of Preformed Xenoantibodies to Porcine Bioprosthetic Valves

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We have investigated whether preformed antibodies against xenoantigens bind to cellular elements remaining on porcine bioprosthetic valves after various methods of preservation. Fresh porcine valves treated with either acetone, 4% formaldehyde, or 0.625% glutaraldehyde, as well as an unfixed valve, were incubated with antiserum against porcine xenoantigens. This serum was prepared using the affinity purification method with porcine lymphocytes as the target. The valves were stained with secondary fluorescein-conjugated antibody against immunoglobulin M or immunoglobulin G and examined under fluorescent microscopy. Intense binding of immunoglobulin M to the endocardium was observed in the unfixed valve as well as in valves fixed in acetone and formaldehyde. Glutaraldehyde fixation eliminated binding of antibody. Binding was not noted within the connective tissue. No binding of antiimmunoglobulin G was noted on the endocardium of any of the sections. Examination of three glutaraldehyde-treated porcine valves explanted from the aortic position after 10 years in situ showed no immunoglobulin deposition. These results demonstrate the elimination of antigenicity to preformed antibodies in the endocardium and connective tissue of glutaraldehyde-preserved porcine valves. The findings may, in part, explain the poor performance of formaldehyde-preserved bioprosthetic xenograft valves in the past and support the use of glutaraldehyde as a preferred agent for preservation of bioprosthetic endovascular materials.

(Ann Thorac Surg 1991;51:30–3)

The late failure of bioprosthetic valves is primarily a consequence of progressive degenerative changes and calcific deposition within the connective tissue collagen ultimately resulting in structural alterations of the valvar cusps [1–4]. Tissue stabilization using glutaraldehyde purportedly eliminates the antigenic potential of heterologous collagen, rendering the tissue biologically inert while also enhancing its durability by protein cross-linkage [5]. Inferential clinical data supporting an immunological role in some bioprosthetic valvar failure have surfaced periodically in the literature yet potential antigenic targets remain speculative and have not been identified [6–10].

The immunologic responses between phylogenetically divergent species such as pig and higher primates are complex and not well understood. This relationship is characterized by the presence of preformed antibodies that simulate a second set response in the absence of previous antigenic exposure and are strongly implicated in the hyperacute rejection encountered in discordant xenogeneic transplantation [11]. The targets for this antibody activity seem to reside on the surface membrane of endothelial cells. We have investigated whether xenoantigens present on the endothelial surface of porcine bioprosthetic valves bind preformed antibody after various methods of preservation.

Material and Methods

Affinity-purified antiserum to pig xenoantigens was prepared from baboon blood. After separation of the cellular fraction, the serum was incubated with pig lymphocytes for 1 hour and centrifuged. The lymphocytes were then resuspended in phosphate-buffered saline solution and the purified antiserum was recovered by elution with acid glycine. The lymphocytes were removed by centrifugation and the supernatant was concentrated using centrifugal evaporation. Frozen sections of fresh pig aortic valve cusps were treated with either 0.625% glutaraldehyde, 4% formaldehyde, or acetone and rinsed in phosphate-buffered saline solution. These, along with an untreated section of fresh valve in phosphate-buffered saline solution, were incubated with the affinity-purified antiserum for either 1 hour at room temperature or 24 hours at 4°C. The valves were then stained with fluorescein-conjugated secondary antibodies to immunoglobulin M (IgM) or IgG (Organon Teknika-Cappel, Malvern, PA) and viewed with an epifluorescence microscope. Binding of affinity-purified serum was evidenced by the appearance of fluorescence under ultraviolet light microscopy.

Glutaraldehyde-preserved, commercially available porcine valves explanted after 10 years in the aortic position in 3 different patients were analyzed. These were removed as a result of primary bioprosthetic valvar failure

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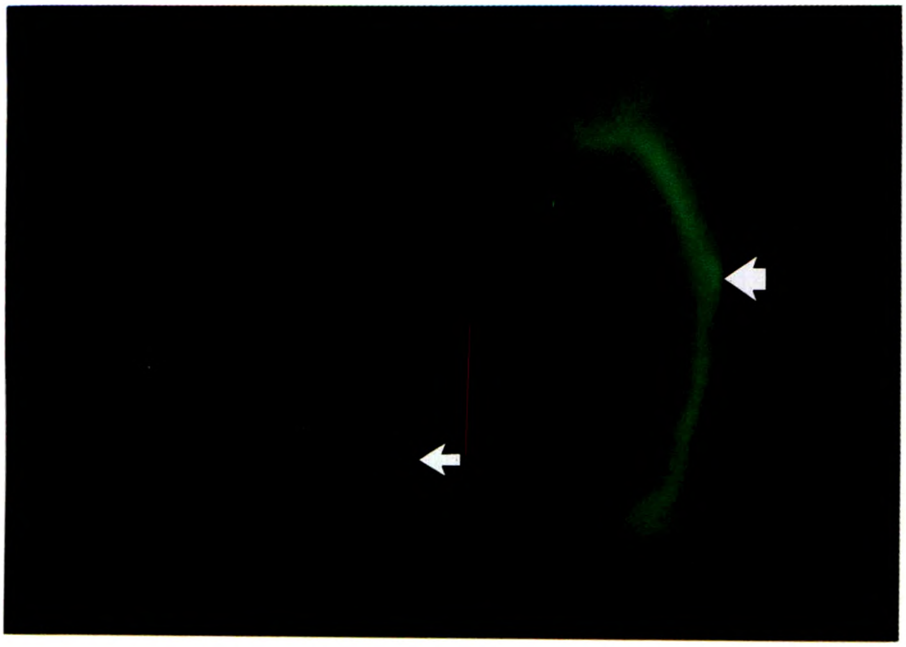

Fig 1. Acetone-treated sections of porcine cardiac valves incubated with affinity-purified xenoantibody followed by fluorescein-conjugated anti–IgM. Note diffuse binding to the endocardial layer (large arrow) *and absence of binding to the connective tissue* (small arrow)*.*

in the absence of endocarditis. The cusps were washed in phosphate-buffered saline solution, stained with secondary antibodies to IgM and IgG, and analyzed as above.

Results

Intense staining of anti–IgM was observed after 1 hour of incubation in untreated sections as well as in sections treated with formaldehyde and acetone (Figs 1, 2). This binding was observed solely on the endocardial layer and was linear along the entire endothelium examined. There appeared to be no binding of anti–IgG in any of the sections stained with this secondary antibody. No specific binding was noted within the connective tissue. The sections fixed in glutaraldehyde did not bind any antibody even after 24 hours of incubation with the antiserum (Fig 3). There was, however, higher autofluorescence, particularly of fibroblast nuclei, in the glutaraldehyde-treated tissue after 24 hours of incubation. No sections stained with anti–IgG antibody demonstrated binding regardless of the method of preservation. The results are summarized in Table 1. The clinically failed and explanted valves did not demonstrate binding of IgM or IgG either

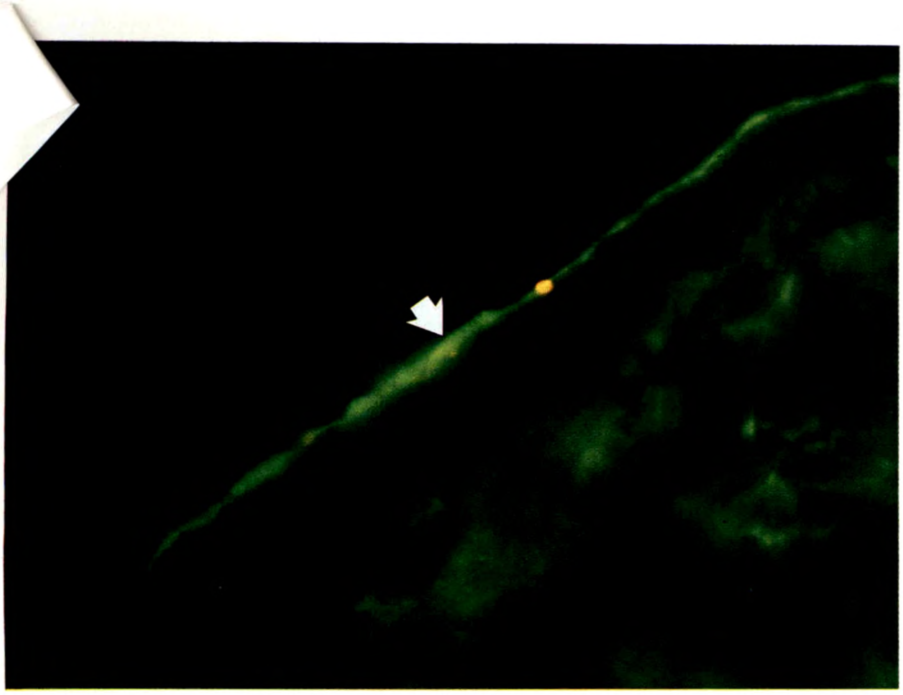

Fig 2. Formaldehyde-treated sections showing binding on the endocardial layer (arrow)*. Autofluorescence in the connective tissue is also noted.*

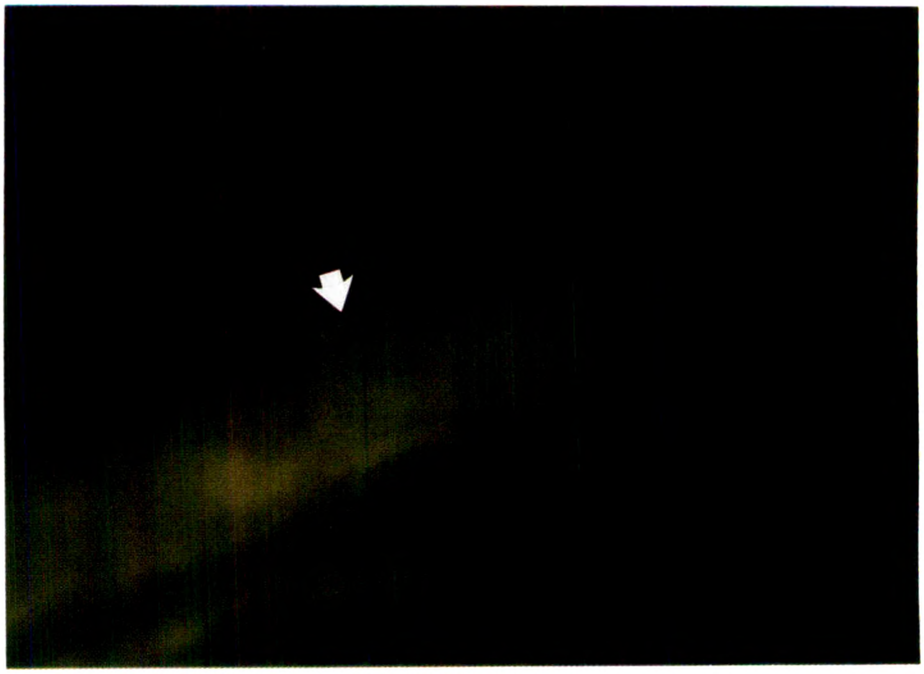

Fig 3. Section of a glutaraldehyde-preserved valve after 24-hour incubation with antisera at 4°C and stained with anti–IgM antibody. Note absence of binding to the endocardium (arrow).

to the remaining endocardium or to any component within the connective tissue. All had calcific deposits by gross visual inspection.

Comment

Since their introduction, the clinical success of valvar bioprostheses has established their suitability as valvar substitutes [12]. However, the superior longevity of mechanical valves has supported their continued use despite the lifelong requirement for anticoagulation and their well-known potential for thromboembolic complications. Suggestions that bioprosthetic failure may be a result of immune mechanisms have been raised by several authors [6–8] on the basis of the presence of immunologically active cells in histological sections of failed bioprosthetic valves as well as elevation of immunoglobulin levels in some patients.

The use of biological materials in the construction of valvar substitutes dates back to 1956 when unprepared aortic valve homografts were employed in both aortic and mitral positions. In 1964, Duran and Gunning implanted in a patient a nonpreserved porcine valve in the aortic position that was recovered unaltered at autopsy 24 hours later [13]. With continued animal studies, however, it became clear that bioprosthetic valves could suffer severe alterations as a result of immunological injury. Attempts to prevent this reaction included immunosuppression with azathioprine as well as the elimination of antigenicity through the use of various agents such as mercurial salts, propiolactone, and highly osmolar sucrose solutions [14–16].

Table 1. Comparison of Results After Incubation of Porcine Valves With Preformed Xenoantibodies With Various Methods of Fixation

Tissue Stabilization	Binding to Endocardium	Binding Within Connective Tissue
None (unfixed)	+	–
Acetone	+	–
4% formaldehyde	+	–
0.625% glutaraldehyde	–	–

+ = binding; – = no binding.

Buffered formaldehyde at various concentrations was employed in an attempt to reduce or eliminate antigenicity and enhance durability by cross-linkage between polypeptide chains in the heterologous collagen. The clinical use of these valves, however, proved disappointing [17]. Their failures were attributed to the reversal of cross-linking within the connective tissue resulting in stretching and rupture of the valvar cusps [18]. With the advent of the glutaraldehyde tanning process, a considerably more durable and presumably less antigenic valvar substitute was produced. The success of this process has been attributed to the relative irreversibility and greater number of cross-links produced as compared with other tissue-stabilizing agents such as formaldehyde [16].

The results of this study indicate that porcine valves preserved through fixation with formaldehyde or acetone retain immunogenicity as evidenced by binding of preformed xenoantibodies to targets on the endothelial cell surface. In comparison, glutaraldehyde fixation appears to eliminate this target. The xenoantigen system in this case served only as a model to investigate the effectiveness of glutaraldehyde and other agents in eliminating antigenic determinants. However, cellular membrane remnants may endure current fixation processes employed in the preparation of commercially available valves and remain within the collagen matrix constituting the bulk of the bioprosthesis. These remnants may provide targets for antibody binding and would result in activation of the complement system with concomitant recruitment of nonspecific immunological mechanisms that ultimately results in damage to the underlying connective tissue in an in vivo setting. This damage may promote the presentation of heterologous collagen to immunologically relevant cells in the recipient and generate primary humoral as well as cellular responses.

The fact that no elements within the connective tissue of the valves appear to attract this antibody response, even in unfixed specimens, substantiates the theory that the preformed antibody response is directed toward structures present on the surface membranes of endothelial cells in vascularized organs. Furthermore, this endothelial binding appears to occur exclusively with IgM, corroborating data suggesting that preformed xenoantibodies are primarily of this class [11].

Examination of valves after 10 years in situ did not demonstrate binding of IgM or IgG antibody either to components within the collagen network or to retained cellular elements. This finding suggests that the use of glutaraldehyde in the tissue-stabilizing process eliminates the antigenic potential of the heterologous collagen contained within the connective tissue matrix, thereby preventing the development of primary humoral immunological responses. Studies of antibody binding on formaldehyde-treated valves explanted after similar periods would be helpful for comparison. Currently, however, their availability is scarce given the relatively small numbers originally implanted and their poor clinical performance.

The antigenic load presented to an organism by bioprosthetic materials such as cardiac valves resides in its collagen network. Cellular elements, however, may also be retained from endothelial cells, myocytes, and fibroblasts. These present a secondary group of antigens that can generate a first-set immunological response. In addition, antigens recognized by preformed antibodies to widely divergent species known to exist in humans create an immediate target. This provided a simple, reliable and rapid method for comparing the antigenic effects of different preservation techniques.

In the case of bioprosthetic cardiac valves, these findings complement the observation that glutaraldehyde fixation results in a marked reduction in antigenicity. This is corroborated by the clinical success of this type of valvar substitute since its inception. The findings may also explain, in part, the poor longevity of the formaldehyde-treated valves, now of historical interest only. In addition, it is important to recognize the differences between formaldehyde and glutaraldehyde treatments on antigenicity when contemplating the development of allogeneic or xenogeneic endovascular bioprosthetic devices. Further understanding of the effects of various tissue-stabilizing processes on antigenicity in these devices may result in the enhancement of durability and diminished failure rates.

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Intrathoracic Nissen Fundoplication: Long-Term Clinical and pH-Monitoring Evaluation

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From 1976 until April 1989, 31 intrathoracic total fundoplications were performed for reflux esophagitis and irreducible hiatus hernia. In the first 16 patients (group 1) the operation was complicated with acute perforation of the wrap in 4 cases, bronchogastric fistula in 1, and herniation of the wrap higher in the chest in 1. Technical modifications were applied to 15 more recent patients (group 2). These are enlargement of the hiatus, looseness of the wrap and its appropriate anchorage, avoidance of forceps when handling the stomach, care with the vagi, and efficient gastric decompression in the postoperative period. The postoperative course was always uneventful in group 2. Twenty-six patients, who still have their initial wrap, were considered for clinical evaluation: 11 from group 1 (mean follow-up, 81.5 months) and 15 from group 2 (mean follow-up, 32.8 months). All are free from any symptom of reflux; gas-bloat syndrome is infrequent and dysphagia is relieved. Twenty-four-hour pH monitoring, performed in 14 patients (3 from group 1 and 11 from group 2) (mean follow-up, 42 months), was normal in 13; a pathological upright reflux (time pH <4, 8.4%) was demonstrated in one symptom-free woman in whom endoscopy was unremarkable. Mechanisms of complications experienced in group 1 are analyzed in the light of the technical evolution of the procedure, and the place of the intrathoracic total fundoplication in the management of short esophagus is defined, considering the other available surgical techniques.

(Ann Thorac Surg 1991;51:34–8)

Gastroesophageal reflux, a common illness in western countries, is sometimes complicated with shortening of the esophagus so that the intrathoracic cardia cannot be replaced below the diaphragm in spite of extensive mobilization of the thoracic esophagus at thoracotomy. A peptic stenosis is frequently associated. Of the different procedures that have been proposed, the intrathoracic Nissen fundoplication has been the most controversial. Conflicting results in terms of efficacy against reflux and postoperative complications have been reported [1–6]. This study reports a 13-year experience with this procedure. Severe complications experienced at the beginning of the series justified technical modifications in performing the operation. The aim of the study is to evaluate both the incidence of these modifications on postoperative morbidity and the long-term clinical and pH monitoring results to know if this procedure still has a place in the treatment of peptic esophageal shortening.

Material and Methods

Population

From 1976 until April 1989, more than 300 adult patients underwent a transabdominal fundoplication for gastroesophageal reflux. Forty-five additional patients were operated on through a left thoracotomy owing to preoperative radiological irreducibility of the cardia down to the abdomen. In these patients, the cardia remained above the diaphragm and the esophagus was not tortuous on roentgenograms taken in the erect position after barium swallow. However, reduction of the cardia could be achieved in 14 of them by extensive mobilization of the esophagus up to the aortic arch, so that a Belsey Mark IV operation was performed in 11 and a subdiaphragmatic Nissen fundoplication in 3. The remaining 31 patients in whom the cardia was surgically irreducible underwent an intrathoracic total fundoplication. Of these, 7 had previously undergone an unsuccessful primary hiatus repair in another institution and 1 had a history of acute mediastinitis resulting from forceful dilations of a narrow stricture. Esophagitis, graduated according to the Skinner-Belsey classification [7], was moderate (grade I or II) in 10 patients and severe (grade III or IV) in 21. Stenoses were preoperatively or intraoperatively dilated using Eder-Puestow dilators.

Operative Technique

The operation (Figs 1, 2) is carried out through a left thoracotomy in the seventh interspace, the eighth rib being cut posteriorly. The esophageal dissection is carried out from the hiatus up to the aortic arch. The pulmonary branches of the vagus nerves are divided at the root of the main bronchi. All esophageal arteries originating from the descending aorta are severed. Care is taken to avoid injury of the vagi, especially in the presence of severe periesophagitis, which can make the dissection extremely difficult. The phrenoesophageal membrane is incised and the abdominal cavity is entered. The fundus is dissected

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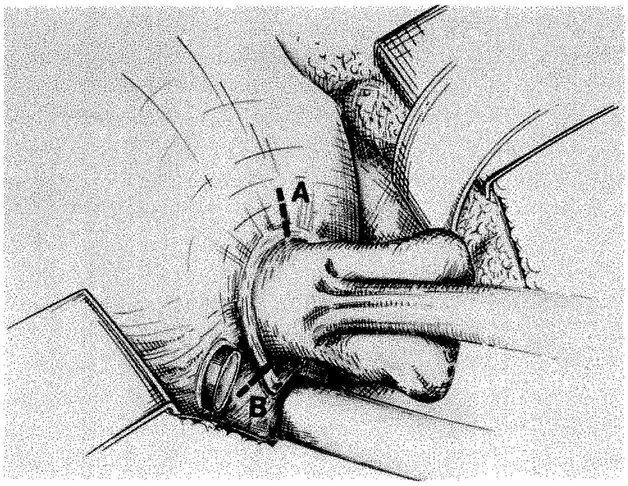

Fig 1. Construction of the intrathoracic wrap (the lower thoracic aorta has been cut away). Dotted line A = *anterior diaphragmatic incision performed radically from the anterior margin of the hiatus.* Dotted line B = *division of the left crus of the hiatus.*

free from the spleen by division of the short gastric veins as well as the upper terminal branches of the left gastroepiploic vessels to bring a large amount of gastric tissue into the chest.

A 5-mm incision is made in the diaphragm forward to the hiatus. A ribbon is passed around the lower esophagus, then downward through the hiatus, and finally upward through the diaphragmatic incision. Gentle traction is exerted on the ribbon in an attempt to reduce the cardia below the diaphragm. This is the best way to assess the surgical irreducibility of the cardia.

The fundus is then wrapped counterclockwise around the lower esophagus so that the suture line is located in the anterior side of the esophagus. A 30F catheter is introduced alongside an 18F nasogastric tube by the anesthetist to avoid any narrowing of the esophageal lumen while performing the wrap. Four to five interrupted nonabsorbable stitches are passed through the seromuscular layers of the left limb of the wrap, through the extramucosal layers of the esophagus, and finally through the seromuscular layers of the right limb. They are tightened gently in order not to tear out the esophageal wall. A second covering row of interrupted stitches is placed over the first row, suturing the two limbs of the wrap. The 30F bougie is removed and the 18F catheter is secured. The wrap is circumferentially anchored to the crura before the chest is closed.

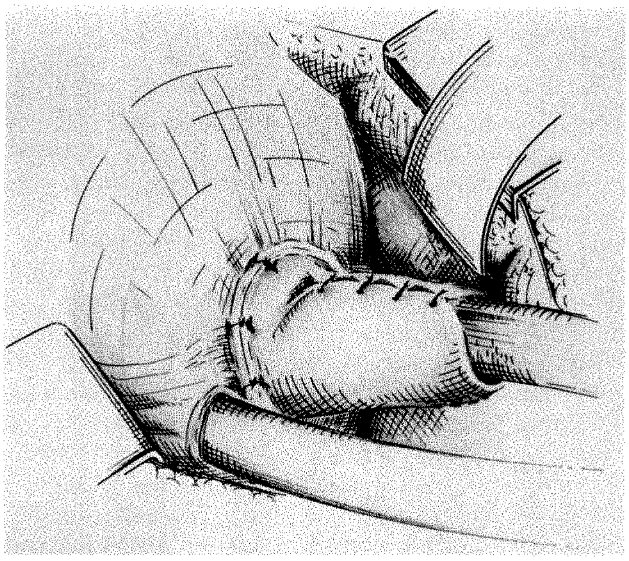

Fig 2. Intrathoracic wrap before closure of the chest.

From 1982, as a consequence of acute complications related to incarceration of the wrap in the hiatus, some technical modifications were introduced: the hiatus, already enlarged by the presence of the hernia, is further widened by dividing the left crus or performing a 3-cm diaphragmatic incision radially from the anterior margin of the crural sling. The stomach is carefully handled with fingers, avoiding the use of forceps and especially the traumatizing Babcock's clamps. The wrap is made as floppy as possible by using more gastric tissue. Particular care is taken to anchor the wrap to the crural sling: with the left hand, the surgeon pushes the left part of the diaphragm down, mimicking diaphragmatic contractions like those that arise on cough, so that the anchorage sites can be precisely marked out on the wrap. The nasogastric catheter is removed only when bowel movements start, and all effervescent beverages are forbidden.

Follow-up

Sixteen patients (group 1) were operated on according to the initial technique and 15 more recent patients (group 2) underwent the modified procedure. Barium swallow was routine in the early postoperative period. Further roentgenographic and/or endoscopic controls were the rule in the later follow-up. All patients still alive, except 4 from group 2, were reviewed by personal interview for the purpose of the study. The most recent available data on the 4 patients lost to follow-up were taken into account. A 24-hour pH monitoring study was performed in patients who accepted it. The probe was located 5 cm above the top of the wrap under fluoroscopic control and further investigations were carried out when any pH abnormality was detected.

Results

Postoperative Complications

There was no postoperative death in any group. In group 1, postoperative morbidity was prohibitive. A spontaneous perforation of the wrap into the chest cavity occurred in four instances and required an emergency thoracotomy, at which it was seen as one or several sharp defects located at a point of the crural anchorage in 1 patient and higher in the wrap in 3. Closure of the defect by a covering suture with maintenance of the wrap was performed twice, but in two other instances the lower esophagus was unwrapped and as much stomach as possible was brought down into the abdomen, resulting in recurrence of reflux. A bronchogastric fistula was not reoper-

Table 1. Results of pH Monitoring in 14 Patients

	% Time pH < 4		
Patients	Supine Position	Upright Position	Total
Group 1			
1	0	8.43	2.85
2	0	1.87	1.13
3	0.01	0.01	0.01
Group 2			
4	0.02	0.48	0.26
5	0.02	0	0.01
6	0.47	0.45	0.46
7	0.25	0.15	0.19
8	0.94	1.01	1.01
9	0.29	0	0.15
10	0.02	0	0.01
11	0	0.02	0.01
12	0	0	0
13	0.43	0.50	0.47
14	0.28	0.32	0.31

ated on. The patient died 5 years later of an unrelated cause, and until her death she was free from any symptom of reflux. Finally, the ascent of the wrap up to the chest justified an esophagogastric resection and a short segment colon interposition in another patient.

In group 2, on the contrary, the postoperative course was always uneventful. One patient was readmitted 8 months postoperatively for a gastric ulcer related to anti-inflammatory medications. It was healed by stopping this therapy and administration of H_2-blockers.

Clinical and pH-Monitoring Results

Of 28 patients who still had their initial wrap, 26, 11 from group 1 (mean follow-up, 81.5 months) and 15 from group 2 (mean follow-up, 32.8 months), are alive. All are free from any symptom of reflux and those who complained of dysphagia preoperatively are able to eat normally. Endoscopic studies demonstrated healing of the stricture, but in the patient with a history of perforation by forceful dilations, a scar persists at the perforation site. Although most patients are unable to belch or vomit, symptoms related to the classic gas-bloat syndrome are infrequent and not disabling in all but 1 patient who experiences uncontrollable rumblings. Her successive barium swallow examinations reveal air distention of the gastric wrap.

Fourteen patients, 3 from group 1 and 11 from group 2, agreed to undergo ambulatory 24-hour pH monitoring. Mean follow-up of the monitored patients was 42 months, ranging from 1 to 139 months (Table 1). The remaining patients refused, arguing the absence of disabling digestive symptoms. Thirteen examinations were normal. In the first patient of this series, pathological acid reflux was detected in the upright position although she was symptom-free and the endoscopic study was unremarkable.

Comment

The intrathoracic total fundoplication is an excellent procedure to control acid reflux related to an irreducible hiatal hernia. Indeed, the preoperative symptoms of reflux were relieved in all patients who still had their initial wrap. Results of pH monitoring were quite satisfactory in all except 1 patient in group 1. On the other hand, strictures healed by endoscopic dilation alone without using a Thal esophagoplasty [8], which adds the risk of leakage at the suture line. Although the length of follow-up was shorter in group 2, it emerges from the present study that the technical modifications we have introduced did not reduce the efficacy of the wrap against reflux. These results confirm those achieved by the abdominal Nissen fundoplication, which has been proved to be more efficient than other procedures [9–11]. The thoracic location of the wrap does not significantly reduce its efficacy [12]. Moreover, the intrathoracic total fundoplication is the only procedure in which the wrap is located above the irreducible cardia.

The main controversy about this operation arose from the severity of the potential postoperative complications. The absence of a phrenoesophageal membrane exposes the wrap to the negative thoracic pressure in such a way that the "organized hiatus hernia" is attracted up to the chest [13]. This situation is completely different from that of an unoperated hiatus hernia, which is located in its sac and remains submitted to positive abdominal pressure. Sudden traction exerted by the diaphragm on the anchorage sites during coughing can tear out the gastric wall. Adhesions and trauma resulting from a previous repair and the sometimes extremely hard inflammation of the mediastinum can make dissection difficult, resulting in damage of the gastric wall and vagal injury. The use of forceps while handling the fundus can also weaken the gastric tissues. Unrecognized truncal vagotomy may be responsible for delayed gastric emptying and impairment of the active relaxation of the stomach, resulting in greater intragastric pressures with lower volumes [14]. A closed-loop phenomenon [6] with subsequent increase in gastric pressure can arise in the case of an intestinal obstruction.

The role of devascularization of the fundus appears to us to be uncertain. Indeed, this devascularization is much less important than that which is performed in a long gastric transplant used as an esophageal substitute after esophagectomy. This gastric transplant is, in its way, a kind of hiatal hernia submitted to negative intrathoracic pressure, but perforation is very rare because of the absence of a valve at the top. Gastric distention and constriction of blood flow to the wrap resulting from snug closure of the hiatus seem more likely to explain acute perforation in the wrap [15]. This situation is similar to the Boerhaave syndrome and requires an emergency thoracotomy. If the patient is reoperated on within the hours that follow the perforation, the defect can be sutured safely with maintenance of the wrap, but delayed rethoracotomy means breakdown of the fundoplication and replacement of as much stomach as possible down to the abdomen after closure of the perforation. Thoracic drainage alone [16] seems to us to be hazardous.

Bronchogastric fistula [4] may be related to the same mechanisms as those that explain free perforation. Our experience suggests that a microfistula can be treated conservatively.

Further herniation of the wrap into the chest is related to the breakdown of the crural anchorage. Mimicking the diaphragmatic movements during the operation appears to be the best way to plan the appropriate anchorage sites.

The gastric ulcer that was diagnosed in 1 patient in group 2 after antiinflammatory therapy healed after administration of H_2-blockers without recurrence and is not likely to be related to incarceration of the wrap. Gastric ulcers were reported after both abdominal and thoracic fundoplications [4] and various causes were proposed: vagal injury [17], gastrin release after gastric distention [18], and bile reflux [19].

The decrease in the complications rate recorded in group 2 suggests the effectiveness of the technical modifications we have introduced. These modifications emerged from our own experience with the group 1 patients. They consisted of enlargement of the hiatus, avoidance of forceps when handling the stomach, looseness of the wrap and its appropriate anchorage in the crural sling, care with the vagi and performing a pyloroplasty if any doubt exists about their integrity, and efficient gastric decompression until bowel movements start.

Various alternative techniques have been described for the management of irreducible hiatus hernias, such as operations carried out from the abdomen [20, 21], forward transplantation of the hiatus [22], acid-reducing procedures [23], and even esophageal resection and colonic interposition [24]. However, the most widely performed operations consist of lengthening procedures, which combine a Collis gastroplasty with a so-called Belsey or Nissen repair [25, 26]. Although generally effective against reflux, these techniques may expose the patient to severe complications [26, 27], and leaving a potentially acid-secretory mucosa above the antireflux procedure is somewhat disturbing. This was advocated to explain esophageal bleeding from ulcers [28], and regression of the normal gastric mucosa to columnar-type cells was documented in the gastroplasty tube [29]. Moreover, five adenocarcinomas arising in the iatrogenic Barrett's esophagus have been reported [30]. For all these reasons, lengthening techniques were not introduced in our institution.

The difficult problem posed by the surgical management of a short esophagus is not entirely resolved today. No technique is ideal. This study proves the high efficacy of the intrathoracic total fundoplication against reflux by both clinical and objective evaluations. Technical modifications that we have introduced have substantially reduced the risk of life-threatening complications. This suggests that this operation has perhaps been prematurely condemned.

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Empyema Thoracis: 14-Year Experience in a Teaching Center

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One hundred two patients with empyema thoracis were managed at the Royal Melbourne Hospital between 1976 and 1989. Fifty-five cases of empyema thoracis were postpneumonic, 8 followed esophageal rupture, and 5 were associated with thoracic trauma. Some form of systemic illness was a major contributing factor in the presentation of 29 patients. A single causal organism was found in 53 patients (the most common being *Staphylococcus aureus*), multiple organisms in 36, and no growth in 13. During the years 1983 to 1989 there was an increased incidence of empyemas caused by multiple or antibiotic-resistant organisms. Operative drainage was required in 90 patients and 12 were managed by thoracentesis or intercostal tube drainage alone. The in-hospital mortality rate for patients managed nonoperatively was 58% (7 of 12 patients); it was 16% (14 of 90 patients) for those receiving operative drainage. There were seven late deaths, four empyema related and three nonrelated. Early adequate operative drainage is recommended for patients with empyema thoracis.

(Ann Thorac Surg 1991;51:39–42)

Empyema thoracis, the collection of pus in the pleural cavity, remains a common and difficult clinical problem. Controversy still exists with regard to how aggressive treatment should be. Some authors rely on initial intercostal tube drainage [1, 2] whereas others advocate early operative drainage [3, 4]. This report describes the Royal Melbourne Hospital experience with empyema thoracis between 1976 and 1989.

Material and Methods

We conducted a retrospective review of 102 patients treated for empyema thoracis at the Royal Melbourne Hospital between January 1976 and December 1989. All patients managed with this condition at the hospital during this period were included. An average of 7 patients were seen each year (range, 4 to 13 per year), with no change in the overall incidence occurring during the 14 years. There were 67 men and 35 women, ranging in age from 18 to 88 years (average, 64 years). The age distribution of these patients is shown in Fig 1.

The common presenting features were fever, chest pain, dyspnea, and cough with or without evidence of systemic toxicity. Few patients were first seen with vague symptoms or were totally asymptomatic. All had clinical signs of a pleural effusion: 52 on the right and 50 on the left.

The primary causes of empyema thoracis seen in this series were as follows: postpneumonic, 55 patients; postoperative, 24; ruptured esophagus, 8; thoracic trauma, 5; septicemia, 4; postpleurodesis, 2; postpleural aspiration, 2; ruptured hydatid cysts, 1; and extension of chest wall suppuration, 1. The causes of 24 postoperative empyemas were pneumonectomy in 11 patients, right middle and lower lobectomy in 3, and right middle lobectomy, left upper lobectomy, coronary artery grafts, mitral valve replacement and coronary artery grafts, esophagectomy, thoracotomy for tracheal tumor, anterior spinal fusion, decortication of mesothelioma, high gastric reduction, and cholecystectomy and bile duct exploration in 1 each. Of the 11 postpneumonectomy empyemas, a bronchopleural fistula was present in eight.

Some form of systemic illness was a major contributing factor in the presentation of 29 patients: rheumatoid disease, 7 patients; insulin-dependent diabetes mellitus, 7; chronic alcoholism, 5; advanced malignancy, 4; chronic malnutrition and debility, 3; chronic renal failure, 2; and systemic lupus erythematosis, 1. No intravenous drug users and no patients with acquired immunodeficiency syndrome were seen in this series.

The diagnosis of empyema thoracis was suspected by the finding of a pleural effusion on chest roentgenogram and confirmed by diagnostic pleural aspiration from which either frank pus was obtained or organisms were grown. The character of the aspirated fluid was noted and it was then sent for Gram stain, microbial culture (both aerobic and anaerobic), and antibiotic sensitivity analysis. Measurements of the pH and glucose and lactate dehydrogenase levels in the pleural fluid were not performed as it was believed that these results did not influence patient management. Computed tomographic scanning was unavailable at our institution early in the series and a computed tomographic scan of the chest was only requested if there was doubt about multiple loculations or the underlying pulmonary parenchymal pathology. Em-

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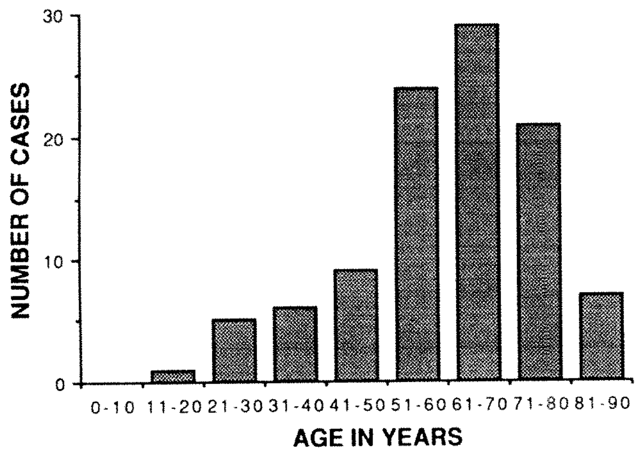

Fig 1. Distribution of age in 102 patients with empyema thoracis.

Table 2. Characteristics of 11 Postpneumonectomy Empyemas

Patient No.	Time to Presentation	Surgical Treatment	Outcome
1	5 d	Flap drainage	Died
2	7 d	Rib resection	Died
3	1 mo	Rib resection	Died
4	1 mo	Flap drainage	Died
5	1 mo	Flap drainage	Alive and well
6	3 mo	Flap drainage	Alive and well
7	15 mo	Flap drainage	Alive and well
8	5 y	Total thoracoplasty	Alive and well
9	5 y	Flap drainage	Late death (CVA)
10	8 y	Flap drainage	Alive and well
11	8 y	Flap drainage	Alive and well

CVA = cerebrovascular accident.

pyemagrams [4] were not used in this series for diagnostic purposes, but were used occasionally for the management of indwelling drainage tubes.

Positive bacterial cultures were obtained in 89 patients. All of the 13 patients with negative cultures were taking antibiotics at the time of or had received a course of therapy before the diagnostic pleural aspiration. The common organisms cultured in all patients are shown in Table 1. From the positive cultures a single organism was identified in 53 patients. Methicillin-sensitive *Staphylococcus aureus* was the most common isolate, being obtained on 22 occasions: 18 single-organism empyemas and four multiple-organism empyemas. Other single organisms frequently found were enterococcus, pneumococcus, and *Klebsiella*.

Multiple organisms were found in 36 patients. An increased incidence of multiple-organism empyemas was noted in the second half of this series. Between 1976 and 1982 only 26% of the positive cultures had multiple organisms, whereas between 1983 and 1989 the incidence of multiple organisms was 52%.

Anaerobic organisms were found in 17% of positive cultures, the majority in combination with other organisms. The methicillin-resistant *Staphylococcus aureus* and fungal empyemas were mostly nosocomial in postoperative or immunocompromised patients. In 12 of the 16 patients with methicillin-resistant *Staphylococcus aureus* isolates other organisms were also found. The incidence of methicillin-resistant *Staphylococcus aureus* empyemas has risen from 7% before 1983 to 22% in the latter half of this series. The laboratory methods for handling empyema fluid were unchanged over the study period.

Table 1. Common Organisms Cultured

Organism	No. of Patients	% of Positive Cultures
Staphylococcus aureus (methicillin sensitive)	22	19
Methicillin-resistant *Staphylococcus aureus*	16	14
Enterococcus	18	16
Pneumococcus	10	9
Klebsiella	10	9
Fungi	8	7
Pseudomonas	6	5
Escherichia coli	6	5
Other organisms	19	17

Results

All patients received antibiotics according to their microbial culture and sensitivity results. Twelve patients were managed by thoracentesis (6) or percutaneous intercostal tube drainage (6) alone. This was successful in 5, but the other 7 (58%) managed in this way died in the hospital. Those who died were immunocompromised or had multiple medical problems and were considered unfit for surgical drainage.

The remaining 90 patients underwent some form of surgical drainage procedure. A rib resection and drainage with a large-bore (36F or 40F) tube was performed in 75 patients, thoracotomy with primary decortication in 5, pleurocutaneous flap in 9, and total thoracoplasty in 1. In 6 of the patients having a rib resection a repeat procedure was required because of incomplete drainage. Those patients with drain tubes in situ postoperatively were managed with progressive tube shortening and regular sinograms on an out-patient basis until the empyema cavity was obliterated. The average drainage period was 11 weeks. Early tube removal (after 5 to 7 days) and cure was obtained in 3 patients with turbid postpneumonic effusions probably sterilized by treatment with antibiotics.

The operative mortality rate for patients treated surgically was 16% (14 of 90). Four of the deaths were in patients with postpneumonectomy empyemas (Table 2). In the operative group there were also seven late deaths: four empyema related and three nonrelated. There was no relationship between the type of organism cultured and the outcome of treatment in this series.

During the 14 years of this series 110 pneumonectomies were performed. The time to presentation, surgical treatment, and outcome of the 11 patients with postpneumonectomy empyemas is shown in Table 2. Six patients were seen within the first 3 months and 4 were seen 5 years or more after pneumonectomy. All came to surgical treatment. Four of the patients seen soon after pneumonectomy died in the hospital from uncontrolled sepsis or multiple system failure.

Comment

Empyema thoracis has been well known to clinicians since the time of Hippocrates. However, following the effective treatment of pulmonary sepsis with antibiotics the appearance of empyema thoracis has been substantially reduced. Despite this, a high incidence of nosocomial and iatrogenic empyemas still exists, as reported in this series. An increasing incidence of empyema thoracis in substance abuse patients has also been noted [5].

The microbial culture results obtained from the pleural aspirates in this series are similar to those of other large series of adult empyema thoracis [1, 3] with *Staphylococcus* and *Streptococcus* species being the most frequently isolated organisms. During the second half of this series we have noted the emergence of methicillin-resistant *Staphylococcus aureus* and fungal infections, especially in the hospital-acquired empyemas. In addition more complex multiple-organism empyemas have been seen. Interestingly, there were no cases of tuberculous or parasitic empyemas.

An aggressive surgical approach was adopted for the majority of patients with empyema thoracis in this series. We believe that once the diagnosis has been made, early adequate, dependent drainage should be achieved by surgical means. The most common procedure was rib resection and drainage (75 patients), with only 5 patients undergoing primary decortication. Decortication has been recommended for the relatively healthy patient in whom intercostal tube drainage is unsuccessful and once the pleural inflammation becomes organized into a fibroelastic membrane [6]. Very few of our patients fell into this category. It is also unclear whether primary decortication results in improved lung function or an earlier discharge from the hospital [6].

Rib resection and drainage allows thorough debridement of the empyema cavity, breakdown of multiple loculations, and the establishment of dependent drainage. Adequate exposure and drainage is facilitated by the use of a headlight, suction, forceps extraction of fibrinous debris, and occasionally thoracoscopy. Intercostal tube drainage is often ineffective especially if the empyema cavity is multiloculated and incompletely entered or the tube (often relatively small, 28F to 32F) becomes blocked. Early use of rib resection and drainage may eliminate the need for later decortication.

The overall mortality in this series was 27%, a figure similar to those of some other reported series [7], although wide variations have been noted. Our patient population is an elderly one (see Fig 1), frequently with chronic underlying disease, and the outcome in these patients is known to be poor. The patients selected for nonoperative management had serious associated diseases or were considered too sick for an operation. As expected the mortality in this group was high (58%). In retrospect, as the results in this group were so poor, these patients could have been managed by rib resection and drainage under local anesthesia.

A number of other methods have been described for the management of empyema thoracis including repeated thoracentesis and the instillation of intrapleural antibiotics [8], thoracoscopy and pleural irrigation [9], and cyclical irrigation of the empyema cavity or postpneumonectomy space [10, 11]. The majority of our patients with postpneumonectomy empyemas were managed by the creation of a pleurocutaneous flap [12]. We have had no experience with open thoracostomy and subsequent closure [13], musculocutaneous flap closure [14], or transmediastinal closure [15] of bronchopleural fistulas or in the use of fibrin sealants introduced endoscopically [16]. These methods have their strong proponents in the literature and we believe they should be reserved for patients with difficult to treat or persistent spaces.

For many years thoracic surgeons have been strong advocates of an aggressive surgical approach to empyema thoracis. In recent times a more conservative approach has crept into the management of this condition. We wish to reemphasize the preferred method of establishing early, complete, and dependent operative drainage. We have been pleased with the results of this simple, standard approach and believe that "the sun should never set on an undrained empyema cavity."

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For this weekend meeting, the Saturday morning segment entitled "Problem Cases" will include panel and audience discussions of four major subject areas: patient selection; anticoagulation management, bleeding, and thromboembolic risk; infections—prophylaxes and treatment; and management of secondary organ dysfunction. An outstanding international panel has been chosen to represent a broad spectrum of opinions for each subject.

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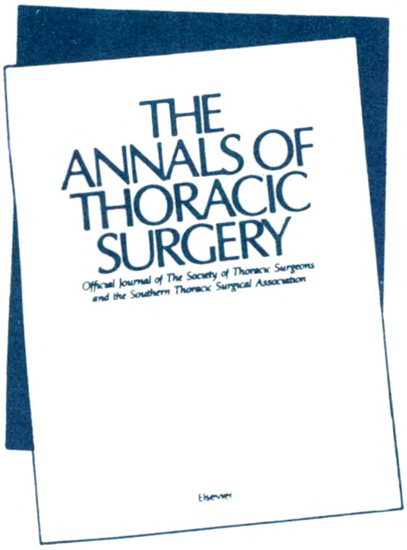

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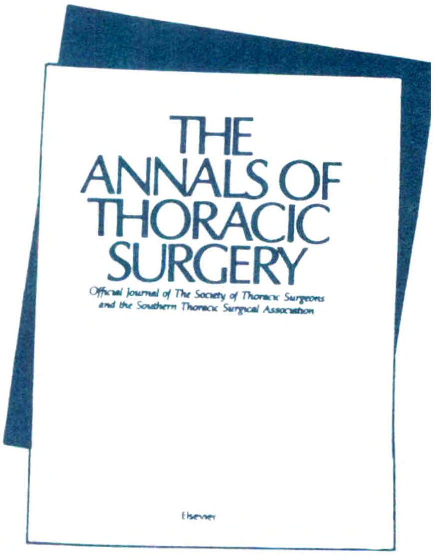

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Mechanical Circulatory Assistance After Heart Transplantation

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From October 1985 through December 1989, 92 heart transplant procedures were performed in 89 patients. Nine patients (aged 19 to 66 years; 7 male, 2 female) required mechanical circulatory support after transplantation because of primary idiopathic organ failure (n = 2), implant difficulty (2), poor organ quality (2), or acute right heart failure (3). Devices used included the intraaortic balloon pump (6), centrifugal right ventricular assist device (2), left ventricular assist (1), biventricular assists (2), and total artificial heart (1). Two patients required multiple devices. One patient underwent retransplantation. Implant time ranged from 1 to 18 days. One early death occurred owing to right heart failure 6 days after transplantation, 7 hours after removal of a right ventricular assist device, for an overall mortality of 11%. The remaining 8 patients are alive 4 months to 28 months after transplantation. The actuarial 1-year survival of 89% ± 10% compares well with the survival of 87% ± 4% for the entire transplant group. All surviving patients are in functional class I. Echocardiographic examination in all patients revealed left ventricular ejection fraction to be normal in 7 and depressed in 1. Extending the criteria for organ donors or difficulty with the implant procedure can lead to early organ failure, which may be reversible with circulatory assistance allowing excellent survival.

(Ann Thorac Surg 1991;51:43–7)

The rapid expansion of heart transplant programs in the 1980s coupled with improved quantity and quality of life have resulted in an increased ratio of patients awaiting transplantation to number of donor organs available. A nationwide donor organ shortage has thus occurred. The necessity to broaden the criteria for organ donors has led to the acceptance of donors of less than ideal quality as compared with those procured under the very strict guidelines of the previous decade. The use of mechanical support devices as bridges to transplantation has also led to increased difficulty in the organ implant procedure itself. Intense scarring secondary to artificial materials in situ for prolonged periods of time coupled with decreased compliance of the mediastinum and shorter vascular cuffs have increased the implant time, thus increasing the probability for organ ischemic damage. Other causes of early transplant organ dysfunction include operative trauma to the donor organ during multiorgan harvest, idiopathic organ dysfunction, right heart failure due to acute, often transient, increases of pulmonary vascular resistance in severe congestive heart failure, and acute rejection [1–3]. If recipient circulation can be supported and hearts transplanted under such conditions can be allowed a period of recovery, excellent long-term function may be expected in these otherwise normally functioning ventricles [2, 4]. If functional recovery does not occur, circulatory support may be accomplished while another organ is sought [5, 6]. This report discusses the experience at the Minneapolis Heart Institute with 9 patients who required mechanical circulatory support after cardiac transplantation.

Material and Methods

The hospital and outpatient clinical records of all patients who required postoperative mechanical support, placed at the initial operative procedure for heart transplantation, were reviewed. Follow-up was conducted by us and is 100%.

Preservation of the donor organ is accomplished using crystalloid hyperkalemic (20 mg KCl/L) buffered cardioplegic solution delivered to the aortic root after exsanguination and decompression of the heart by division of the left pulmonary vein and of the inferior and superior vena cavas followed by aortic cross-clamping. Donor cardiectomy and transplantation are performed using standard techniques.

Weaning from cardiopulmonary bypass (CPB) is conducted using right atrial pressure monitoring. If dysfunction of either ventricle is suspected a left atrial monitoring line is inserted. Before the patient is weaned from CPB isoproterenol is infused at a dose of 1 to 4 μg/min to maintain heart rate at 100 to 120 beats/min and dopamine is infused at 3 to 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the face of left ventricular (LV) dysfunction dobutamine and then epi-

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Table 1. Patient Data

Patient	Recipient Age (y)	Donor Age (y)	Ischemic Time (min)	Device Used	Device Duration (d)	Cause of Cardiac Dysfunction	Hospital Stay After Tx (d)	Survival
JH	61	43	276	RVAD	7	Right ventricular failure, long ischemic time	NA	–
DB	53	40	160	IABP	1	Idiopathic	13	+
DM	19	30	118/210	IABP, BIVAD, Symbion J-7-70	18	Idiopathic	17	+
BK	19	40	255	IABP, BIVAD	4	Difficult implantation	63	+
PH	66	47	265	IABP	2	Marginal donor quality	15	+
JK	60	47	76	LVAD	4	Marginal donor quality	21	+
SS	53	34	180	RVAD	14	Right heart failure	30	+
BR	63	23	96	IABP	1	Right heart failure	10	+
EB	45	41	206	IABP	4	Difficult implantation	11	+

BIVAD = centrifugal left and right ventricular assist devices; IABP = intraaortic balloon pump; J-7-70 = Symbion J-7-70-mL-ventricle total artificial heart; LVAD = centrifugal left ventricular assist device; RVAD = centrifugal right ventricular assist device; Tx = transplantation.

nephrine are sequentially added; in patients with right ventricular dysfunction, dobutamine and amrinone are used. Mechanical assistance is instituted when indicated by continued ventricular dysfunction before excessive doses of inotropic or pressor agents. Mechanical support is added sequentially from the simplest (intraaortic balloon pump [IABP]) to more complex forms (centrifugal ventricular assist device [VAD]/total artificial heart) as dictated by cardiac function.

The patients were managed with triple-drug immunosuppression. Those patients having centrifugal devices or Symbion J-7-70 artificial heart, as well as patients with secondary organ system dysfunction while on device support, were treated with induction immunosuppression and steroid discontinuation [7]. Values are expressed as mean ± standard error of mean and actuarial data are by the method of Cuttler-Ederer or Kaplan-Meier calculations.

Results

From October 1985 through December 1989, 92 heart transplant procedures were performed in 89 patients. Nine patients aged 19 to 66 years required mechanical circulatory support because of donor organ failure after transplantation. The cause of organ failure was varied. Three patients suffered acute right ventricular failure, and 2 patients each received organs that were believed to be compromised before the transplant procedure, had organ failure of unidentified cause, or had prolonged implant time because of extreme difficulty with the operative procedure. There were no intraoperative deaths in the entire series.

Devices used for postimplantation support included the IABP in 6 patients, centrifugal right VADs in 2 patients, left VAD in 1 patient, biventricular assist devices in 2 patients, and the Symbion J-7-70 total artificial heart in 1. Mean time of implantation of the device was 7 ± 2 days with a range of 1 to 18 days. Because of the varied nature of the indications for devices and the devices used, a brief patient history is described. Patient demographics are delineated in Table 1 in order of occurrence.

JH was a 63-year-old man with ischemic cardiomyopathy. Preoperative pulmonary vascular resistance was 4.5 Wood units. The patient became intensive care unit–bound in severe congestive heart failure and an acute increase in the pulmonary vascular resistance to the range of 6 to 7 Wood units was calculated. An organ became available and, after an uncomplicated implant procedure (preservation time of 276 minutes), the patient was unable to be weaned from CPB because of right ventricular dilatation associated with falling left atrial pressure and systemic hypotension. A centrifugal right VAD was placed using right atrial appendage outflow and pulmonary arterial inflow. After 7 days, right ventricular function appeared to improve and the patient was slowly weaned from the device, which was subsequently removed. Seven hours after removal of the device, the patient had abrupt hypotension associated with markedly increased right atrial pressure and, soon thereafter, cardiac arrest. He was unable to be resuscitated.

DB is a 61-year-old man who underwent elective transplantation. After an organ ischemic time of 160 minutes, poor LV function prevented weaning from CPB. An IABP was percutaneously placed and, after a rest period on

CPB, weaning was readily undertaken. The IABP was removed the following day. One-year follow-up catheterization revealed normal ventricular function and the patient is in functional class I 28 months postoperatively.

DM is a 20-year-old man with congenital concentric hypertrophic cardiomyopathy and sudden death syndrome. Elective transplantation was undertaken. In spite of an uncomplicated organ harvest and implant procedure, and a short ischemic time (90 minutes), biventricular function was never obtained. After 6 hours of CPB support, centrifugal biventricular assist devices were placed (right atrium to pulmonary artery and left atrium to aorta). After 12 hours of support, a paced rhythm was established but no pressure function could be generated. This heart was excised and a Symbion J-7-70 total artificial heart was implanted. After an 18-day implant period, a second donor organ was transplanted. The patient made an uncomplicated transplant recovery and is currently a college student 24 months after transplantation without limitation. One-year follow-up catheterization revealed normal LV function.

BK, a 20-year-old man with end-stage congestive cardiomyopathy, underwent placement of a Symbion J-7-70 total artificial heart as a bridge to transplantation because of progressive cardiogenic shock and secondary organ system dysfunction. A complicated course on the Jarvik-7 was culminated with organ transplantation. A large donor organ was implanted with great difficulty owing to dense mediastinal adhesions, a decrease in mediastinal compliance, and small posterior atrial cuffs. A long ischemic time resulted (255 minutes). After a prolonged resuscitation, LV pressure function was never able to be generated and an IABP was placed. Subsequently poor biventricular function obviated cessation of CPB. Biventricular centrifugal support devices were placed (right atrium to pulmonary artery; left atrium to aorta). The support devices were discontinued on postoperative day 4 and the IABP on day 5. The patient is 17 months after transplantation, is without limitation, and has normal LV function at 1-year catheterization.

PH is a 67-year-old man with end-stage ischemic cardiomyopathy after two prior coronary artery bypass procedures. Acute cholecystitis necessitated cholecystectomy and in the postoperative period, progressive congestive heart failure required stabilization with IABP placement. In spite of inotropic therapy, the patient was unable to be weaned from the IABP over 3 weeks. Because of the patient's age and his debilitated condition, transplantation was offered only under the condition that an organ be used that was otherwise turned down by all programs to which it was offered. A 47-year-old donor organ from a patient with a 20-year history of insulin-dependent diabetes mellitus became available. Echocardiographic function of the donor organ was normal. The donor site was 2,400 km (1,500 miles) from the transplant center. At the time of harvesting only the heart was procured as all other organs had been turned down for donation. After an ischemic period of 265 minutes and prolonged resuscitation, LV function was marginal. The preoperative IABP was maintained and used until postoperative day 2, when it was removed. The patient is without restriction 17 months after operation. Echocardiographic study reveals normal organ function.

JK is a 61-year-old man with ischemic cardiomyopathy. The patient, of large body size and blood type O, had progressive left ventricular failure and secondary organ system dysfunction. Because of limited organ availability a prolonged waiting time was expected. A local organ donor with a history of severe systemic hypertension became available and echocardiographic examination revealed concentric hypertrophy of the ventricle. At the time of organ harvest, a large, globular, concentrically hypertrophic organ was transplanted with an ischemic time of 76 minutes. Poor LV function after resuscitation necessitated insertion of a centrifugal left VAD (left atrium to aorta). The device was removed on postoperative day 2. Sixteen months after transplantation the patient has no restriction and 1-year catheterization reveals normal system function although LV filling pressures are elevated at 24 mm Hg.

SS is a 53-year old woman with preoperative pulmonary vascular resistance of 4 Wood units. She suffered severe congestive heart failure and was intensive care unit-bound before her transplant procedure. After transplantation, CPB was unable to be discontinued because of right ventricular failure associated with systemic hypotension and low left atrial pressure. A centrifugal right VAD was placed (right atrium to pulmonary artery). The patient was extubated on postoperative day 4 with the right VAD in place. The patient was able to be mobile in bed with the right VAD. Transesophageal echocardiography was used every third day to follow up right ventricular function and, after 14 days, the patient was able to be weaned from the device, which was discontinued. Fourteen months after operation echocardiography reveals an LV ejection fraction of 0.57.

BR is a 63-year-old woman with end-stage ischemic cardiomyopathy and pulmonary vascular resistance of 6.5 Wood units. Elective transplantation was performed (ischemic time, 96 minutes), and with discontinuation of CPB, right ventricular dilation occurred with progressive elevation of right atrial pressure. The patient was immediately replaced on full CPB support with cardiac decompression, and an IABP was placed. After a further period of resuscitation, CPB was gradually weaned with IABP and inotropic support. The IABP was discontinued the first postoperative day and the patient was discharged on postoperative day 9. Echocardiogram on postoperative day 10 revealed normal biventricular function. The patient is without restriction 5 months after transplantation.

EB is a 45-year-old man with end-stage cardiac failure after two coronary revascularizations, the last including internal mammary artery grafting and LV aneurysm repair 10 months before transplantation. At the procedure, dense mediastinal adhesions and a fibrotic, noncompliant mediastinum coupled with a large donor organ created a difficult and prolonged implant procedure resulting in a total ischemic time of 189 minutes. After revascularization, LV function was marginal and left atrial pressure elevated on inotropic support. One attempt at discontinuation of CPB failed. An IABP was placed and CPB gradually discontinued. Postoperatively diastolic dysfunction was found on echocardiography (left atrial pressure, 23 to 28 mm Hg) with abnormal systolic function (ejection fraction, 0.33). After 3 days of IABP support LV function improved (ejection fraction, 0.45), left atrial pressure decreased to 13 to 15 mm Hg, and diuresis ensued. The IABP was removed on posttransplantation day 5. The patient was discharged on posttransplantation day 11 and has normal function 5 months after transplantation.

The posttransplantation course in these patients was more complicated than routine, the mean posttransplantation stay being 24 ± 17 days (range, 10 to 63 days). The patient with the most complicated course was a 19-year-old bridged to transplantation and supported with a biventricular assist device after transplantation.

Two patients had three bacterial infections, all in the first month after transplantation, and were treated using the appropriate antibiotics. There were no surgical wounds involved. In 1 patient (BK) an infected sacral decubitus ulcer requiring surgical closure and a urinary tract infection developed; the other patient had an infected sebaceous cyst. Systemic cytomegaloviral infections developed in 3 patients in the second posttransplantation month, and fungal infection developed in 2 patients in the first month after transplantation (1 patient had fungal infection contaminating a sacral ulcer and a second patient had vaginitis). There were eight infections in 7 patients for an incidence of 1.2 episodes/patient. Three rejection episodes occurred in 2 patients at 1 month, 3 months, and 15 months after transplantation. The actuarial freedom from rejection is 67% ± 19% at 1 year. Eight patients survived the operative procedure for an operative mortality of 11%. The actuarial 1-year survival is 89% ± 10%, which compares favorably with the results from our overall series of 87% ± 3% over this period. Renal function measurement at 6 and 12 months after transplantation revealed a blood urea nitrogen level of 9.3 ± 1.1 and 7.5 ± 0.2 mmol/L of urea (26 ± 3 and 21 ± 0.5 mg/dL), respectively, and the creatinine level was 115 ± 18 and 106 ± 44 μmol/L (1.3 ± 0.2 and 1.2 ± 0.5 mg/dL). Seven surviving patients are in functional class I and 1 is in class II 4 months to 28 months after transplantation. Echocardiographic fractional shortening of the left ventricle at the most recent examination is 0.36 ± 0.03 with a range of 0.28 to 0.42 (normal, 0.28).

Comment

In addition to idiopathic donor organ dysfunction, operative trauma, right heart failure, and organs removed from donors with suspected sepsis, the causes of donor organ failure are few [8]. Donor organ failure is uncommon, but in the current era of organ shortage, the use of less ideal donors has become necessary and formerly used strict donor criteria have been liberalized [9]. Older organ donors, organ donors with mild ventricular dysfunction, and those with systemic infection have been used with good results [10–12]. Primary donor organ failure has been associated, albeit uncommonly, with the use of older and less ideal donor organs, longer ischemic times, and more difficult implant procedures associated with reoperative open heart procedures and with the use of mechanical assist devices as bridges to transplantation. Ventricular function abnormalities occur in patients with high-grade neurologic injuries and may contribute to cardiac dysfunction after organ transplantation [13]. Although controversial, prolonged ischemic times have been negatively associated with both short-term and long-term patient survival [8, 14, 15]. We have come to realize that the donor heart suffers from a period of injury owing to both operative trauma during multiorgan harvest and the relatively warm ischemic time during implantation, but it can recover if circulatory support can be maintained to allow recovery time.

Mechanical circulatory support, first used in the 1960s for postcardiotomy cardiac failure, has come to age in the 1980s with sophisticated devices used to allow myocardial recovery, for bridging to transplantation, or as permanent replacement organs [16]. Mechanical bridges between transplants has been rarely accomplished successfully using either the total artificial heart or VAD support [6] (Copeland JG, Griffith BP, personal communication, 1990). Kanter and associates initially reported limited success with mechanical support to organ recovery after transplantation, but with experience gained, successful recovery of dysfunctional transplanted organs using left and right VADs and biventricular assist device support has been reported as isolated cases [1, 2, 4, 17, 18]. Long-term function and rehabilitation of such patients has not been documented. This series demonstrates excellent late function in patients who have returned to the mainstream of life following the use of mechanical circulatory support after transplantation. In a series of 89 transplant patients over 4 years, we have used 12 organs from nontraditional donors in high-risk or critically ill patients, including organs from patients aged 45 to 58 years, organ donors with risk factors to cardiac disease such as diabetes mellitus, organ donors with known myocardial disease (urgent situations), and organ donors with unusual causes of death such as strangulation or carbon monoxide poisoning. Four (33%) of these organs have required myocardial support after transplantation and 10 of these patients have survived long term. Five (6%) other patients from traditional donors required mechanical support and have survived. One donor suffered carbon monoxide poisoning; after transplantation, excellent function was immediate as opposed to the experience of others [19]. With posttransplantation use of aggressive inotropic and mechanical support in the face of normal organ donor echocardiographic and clinical examination, we believe the use of such marginal donors is possible in critically ill or high-risk transplant patients.

Several lessons have been learned from this experience. (1) As reported by others, cardiac catheterization should not be routinely used in organ donors as it may compromise cardiac function and rule out organ donation as opposed to rule in coronary disease [11]. The use of the electrocardiogram and echocardiographically determined ventricular function coupled with thorough examination of the heart at the time of organ donation suffice. (2) Patience in the resuscitation after reestablishment of blood flow is of import. The use of inotropic support should be withheld until the heart has had a sufficient recovery period and is warmed. A distention injury of the heart during the resuscitation period is a serious injury. Prolonged bypass support may be necessary to gain organ function. (3) The IABP is probably most useful as an afterload-reducing device as opposed to augmenting coronary blood flow in these often normal hearts, especially in patients with right ventricular dysfunction. (4) The recognition of right heart failure must be made early to prevent further injury to the already weakened right side of the heart, and the appropriate form of support should be applied. (5) Support of the left ventricle should be undertaken early, and progression from simpler devices to the more complex is warranted. Left ventricular support devices such as the IABP and left VAD may be useful in lowering left atrial pressure and therefore improving right ventricular function. The use of LV support alone in the face of biventricular failure has been successful. A new device, the Nimbus Hemopump, has been used successfully to support the failing transplanted heart and may prove to be a very useful device in the future [3]. (6) The transesophageal echocardiogram is a reliable tool for following up ventricular function and preventing weaning from a device before organ recovery has occurred. Absence of functional recovery would indicate irreversible injury and another organ may be sought. (7) Prolonged mechanical support may be necessary and can safely be accomplished.

We believe that aggressive measures of myocardial support are warranted in patients in the posttransplantation period should univentricular or biventricular dysfunction occur. A variety of devices are available and the simplest device that will support the patient's circulation should be used.

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Multiple Primary Bronchogenic Carcinomas: Treatment and Follow-up

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A second primary bronchogenic carcinoma subsequently developed 8 to 156 months later in 19 patients who underwent curative resection of primary bronchogenic carcinomas. The second primary tumor was treated by surgical resection in 9 patients, 3 patients' tumors were considered unresectable, and the remaining 7 patients, despite having potentially resectable tumors, did not undergo resection because of insufficient pulmonary reserve or unwillingness to undergo resection. Actuarial life-table analysis of survival for the 9 patients who underwent resection showed a median survival time of 110.3 months compared with 19 months for the group with unresected but resectable tumors and 10.5 months for the group with unresectable tumors. There was no operative mortality in the group with resected tumors. We conclude that in patients in whom a second primary carcinoma of the lung develops, surgical resection prolongs survival and can be performed with a low operative mortality.

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Multiple primary bronchogenic carcinomas are rare [1–5] especially compared with tumors in other paired organs such as breast or ovary. This is surprising in view of the high rate of bronchogenic carcinoma in the general population and the fact that the inhaled carcinogens responsible for the primary lung cancer in the first place must also act on the entire respiratory epithelium. In the past this rarity may have been due to some patients in whom new lung densities developed and who were assumed to have recurrent or metastatic disease and were treated as such without a definitive diagnosis being sought. Other patients were lost to follow-up or died of other causes without autopsy study. The most likely explanation is that the overall survival of patients with lung carcinoma is so low that there may not be enough time for a second primary tumor to develop [6]. This low survival has also led to a somewhat cautious approach to the management of patients with multiple primary bronchogenic carcinomas. Although resection is generally considered the optimum treatment when possible, it has not been shown conclusively to improve survival when patient undergoing resection were compared with patients of similar stage who have not undergone resection [3, 4, 7, 8]. This study describes 19 patients in whom second primary lung cancers developed over a 16-year-period and compares survival rates between those who underwent resection and those who did not.

Material and Methods

This study includes 19 of approximately 1,700 patients treated by surgical resection for bronchogenic carcinoma in whom second primary lung cancers developed over a 16-year period (operated on and followed up by the senior author [C.L.N.R.]). The criteria used for the diagnosis of metachronous lung cancers were those established by Martini and Melamed [1]. These included: (1) tumors of different histological structure and (2) tumors of same histological structure with (a) time interval between tumors of at least 2 years or (b) origin from carcinoma in situ or (c) tumors that were anatomically separate and in which lymphatic involvement and extrapulmonary metastases were reasonably excluded.

The charts were reviewed and the following information was obtained: age, sex, occupation, smoking history, operation, tumor histology, stage and TNM classification of first and second tumors, time interval between tumors, method of diagnosis, treatment and survival after diagnosis of the second tumor. Follow-up period was until January 1989. The tumors were staged according to the new international staging system for lung cancer [9]. Statistical analysis using the Lee-Desu statistic and the actuarial life-table analysis was performed to determine whether the time interval between tumors or the choice of therapy of the second primary tumor had any prognostic value.

Results

There were 16 male and 3 female patients with ages ranging from 50 to 73 years (median, 64 years). All but 1 patient had a smoking history and 3 patients had an occupational risk factor for lung cancer. Six patients had a previous nonpulmonary cancer (laryngeal carcinoma, 2; basal cell carcinoma, of the skin, 2; bladder carcinoma, 1; and colon carcinoma, 1) and were considered cured of these tumors before their bronchogenic carcinomas were diagnosed.

The locations of the first primary bronchogenic carcino-

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Table 1. Anatomical Locations of Multiple Primary Lung Tumors

Lobe	First Tumor (n)	Second Tumor (n)
Right upper	5	7
Right middle	2	1
Right lower	5	1
Left upper	5	6
Left lower	2	4

Table 3. Tumor Cell Types

Histological Structure	First Tumor (n)	Second Tumor (n)
Squamous	11	9
Adenocarcinoma	7	5
Large cell	1	1
Non–small cell	. . .	3
Small cell	. . .	1

mas are shown in Table 1. Eighteen patients had stage I and 1 patient had stage II lung cancer (Table 2). The most common tumor histology was squamous followed by adenocarcinoma (Table 3). The first primary tumors were all treated by surgical resection. The operations included: pneumonectomy, 1; bilobectomy, 1; lobectomy, 16; and segmentectomy, 1. The diagnosis of the second primary lung cancer was suspected based on cytological examination of the sputum and chest roentgenogram in 2 patients, bronchoscopy and chest roentgenogram in 3, and roentgenogram only in 14. The locations of the second primary tumors are shown in Table 1. All patients with primary tumors in the right upper lobe had contralateral second tumors (left upper lobe, 4; left lower lobe, 1). Both patients with right middle lobe tumors had second primary tumors in the right upper lobe. Of the 5 patients with original tumors in the right lower lobe, 3 had second primary tumors occurring in the left upper lobe, 1 in the right upper lobe, and 1 in the right middle lobe. Four of the 5 patients with primary tumors in the left upper lobe had a contralateral second tumor (right lower lobe, 2; right upper lobe, 1; right middle lobe, 1) and 1 had an ipsilateral second tumor (left lower lobe). The 2 patients with left lower lobe tumors both had contralateral second primary tumors (right upper lobe and right lower lobe).

Tissue confirmation was obtained by thoracotomy, needle aspiration, bronchoscopy, and mediastinoscopy. Of the 11 patients with squamous carcinoma first primary tumors, the histological structure of the second tumors was as follows: squamous, 5; non–oat cell, 3; adenocarcinoma, 1; small cell, 1; large cell, 1. Squamous carcinoma second primary tumors developed in 3 of the 7 patients with an adenocarcinoma first primary tumor, and adenocarcinoma second primary tumor developed in the remaining 4 patients. The single patient with a large cell carcinoma had a squamous carcinoma second primary tumor. The histological structure of the first and second tumors was different in 7 patients.

Table 2. Stage of First Primary Tumor

Stage	TMN Classification	n
I	T1 N0	11
	T2 N0	7
II	T2 N1	1

The time interval between first and second primary bronchogenic carcinomas was less than 1 year in 3 patients, 1 to 3 years in 6 patients, 4 to 12 years in 9 patients, and greater than 13 years in 1 patient.

The second primary tumor was treated by surgical resection in 9 patients. The procedures included: completion pneumonectomy, 2; lobectomy, 1; segmentectomy, 4; and subsegmentectomy, 2. There was no operative mortality. The pathological stage after resection of the second primary tumor is as follows: 7 patients, stage I; 1 patient, stage II; and 1 patient, stage IIIa bronchogenic carcinoma.

Ten patients had second primary tumors that were not resected. Three patients had tumors that were considered unresectable (stage IIIb, stage IV, oat cell carcinoma) and therefore not candidates for operation. However, 7 patients had potentially resectable tumors (stage I or II, 6; stage IIIa, 1) but did not undergo operation because of insufficient pulmonary reserve (1) or patient refusal (6) of a second operation.

The time interval between tumors ranged from 8 to 156 months. There were 9 patients with an interval between tumors of less than 4 years with a median survival of 46 months. A comparison of these survival data using the Lee-Desu statistic showed no statistical significance. Actuarial life-table analysis of survival for the 19 patients showed a median survival time of 38.6 months. There was 78% survival at 6 months; 68.4% at 12 months, 52.6% at 2 years, and 32.3% at 5 years.

The 19 patients were grouped into three tumor categories for survival analysis: surgically resected, resectable but not operated, and unresectable (Table 4). The difference in survival of the group with surgically resected tumors versus the group with resectable but nonoperated tumors was statistically significant ($p = 0.003$). A graph plotting percent survival against follow-up in months of

Table 4. Survival After Diagnosis of Second Primary Lung Cancer

Tumor Operability	n	Median Survival (mo)[a]
Resected	9	110.3
Resectable	7	19
Unresectable	3	10.5

[a] Lee-Desu = 9.4; $p = 0.009$.

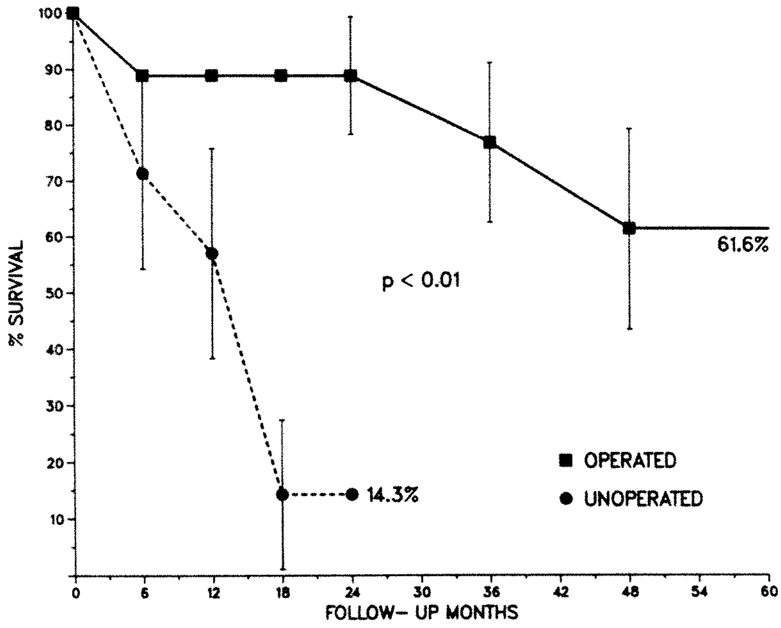

Fig 1. Actuarial life-table analysis of the patients with second primary lung tumors that were resected or with potentially resectable tumors on which operation was not performed.

these two groups is shown in Figure 1. Three patients in the surgically resected group have been followed up for at least 5 years.

Comment

This study shows that in patients in whom second primary carcinoma of the lungs develops, surgical resection is the treatment of choice. This approach is associated with a low operative mortality and relatively long survival when compared with no resection in patients with similarly staged lung carcinomas.

It is often impossible to state with certainty whether a second tumor is indeed a new primary lesion. In the present study, using the criteria established by Martini and Melamed [1], problems still arise. Many lung tumors show diverse histological types in single tumors [10,11]. A time interval between tumors of at least 2 years may preclude consideration of synchronous tumors as separate independent primary tumors, and the origin from carcinoma in situ is not clear-cut in all tumor types. Allied to this is the growing impression that differentiating whether a new tumor is a new primary or a recurrence is irrelevant to its management [12–14]. The more important question is whether surgical intervention in these situations prolongs life.

In this study, the median survival for patients who underwent lung cancer resection was 110 months compared with 19 months for those who had resectable tumors but did not undergo resection and 10.5 months for those who had unresectable tumors. The preoperative staging did not significantly differ between the first two categories. Of the patients who had resectable tumors but did not undergo resection, 6 refused operation for personal reasons whereas 1 was regarded as unsuitable for operation owing to pulmonary function limitation. It is unlikely that pulmonary function accounted for the large differences in survival.

Our results differ from others in the literature. Actuarial life-table analysis of survival for all our 19 patients (with resected and unresected tumors) showed 78% survival at 6 months, 68% survival at 12 months, 53% survival at 2 years, and 32% survival at 5 years. These figures are very close to those reported by Salerno [15] and Jensik [3] and their associates for patients with resected tumors alone. Our patients with resected tumors had 89% survival at 12 months, 89% survival at 2 years, and 62% survival at 5 years. The reasons for this are not immediately apparent. There is no significant demographic difference between our study group and others in the literature [1–6]. The time interval between tumors ranged from 8 to 156 months, which is not significantly different from that of other studies. Time interval between tumors did not affect survival in our study as the median survival in the 9 patients with an interval between tumors of less than 4 years did not significantly differ from that in the 10 patients with an interval between tumors of greater than 4 years. It is not surprising that the second procedures were more conservative lung cancer operations than the first. This results in the preservation of lung function and allows resection in select patients with borderline pulmonary function.

In summary, this study shows that in patients in whom second primary carcinoma of the lung develops, limited surgical resection offers the best treatment, being associated with a low operative mortality and prolonged survival. This study, along with others, shows that in lung cancer the concept of cure in patients who are disease-free after 5 years may be erroneous and mandates close lifelong follow-up of all patients who have undergone resection for bronchogenic carcinoma.

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Hemodynamics Versus Biopsy Findings During Cardiac Transplant Rejection

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Before the use of cyclosporine as the major component for immunosuppression after cardiac transplantation, rejection was accompanied by catastrophic hemodynamic decompensation. However, the hemodynamic changes that occur during rejection after cardiac transplantation in patients treated with cyclosporine have not been clearly described. Between July 1986 and October 1989, 89 adults underwent orthotopic heart transplantation at the University of Michigan Medical Center. All patients received triple-drug therapy immunosuppression consisting of steroids, cyclosporine, and azathioprine. Cardiac hemodynamics were measured and correlated with the histologic assessment of rejection. There have been ten deaths among these 89 patients for an overall survival of 89%. There were no deaths from rejection. One hundred fifty-three of the biopsy specimens were read as grade 0, 31 were grade 1, 75 were grade 2, 103 were grade 3, and 9 patients had grade 4 biopsy specimens. No hemodynamic differences were noted in patients with increasing grade of rejection. Five patients (5/9, 55%) with severe rejection (grade 4) had symptoms of congestive heart failure at the time of biopsy. These symptomatic grade 4 patients differed from asymptomatic grade 4 patients only in cardiac output (2.9 versus 5.2 L/min). Overall hemodynamic decompensation was not evident as rejection grade increased. Routine serial endomyocardial biopsies remain the procedure of choice in the diagnosis of rejection in the asymptomatic patient after cardiac transplantation as hemodynamics do not predict degree of rejection.

(Ann Thorac Surg 1991;51:52–5)

Before the introduction of endomyocardial biopsy for monitoring rejection in patients undergoing orthotopic cardiac transplantation, rejection was diagnosed clinically by the onset of electrocardiographic changes, arrhythmias, and hemodynamic decompensation [1–3]. As few patients survived severe symptomatic rejection episodes, there was a critical need for a method to diagnose rejection before the onset of symptoms.

The endomyocardial biopsy introduced in 1975 [4] quickly became the standard for the diagnosis of rejection in patients after cardiac transplantation. This allowed the early detection of rejection and avoided severe hemodynamic decompensation. However, the hemodynamic changes that accompany rejection in patients treated with cyclosporine as a major component of their immunosuppressive regimen have not been clearly defined. Right heart catheterization is commonly performed simultaneously with endomyocardial biopsy, to delineate the hemodynamic function of the transplanted heart. We have correlated the hemodynamic function of the transplanted heart in patients treated with cyclosporine, with the histologic grade of rejection from the simultaneously obtained endomyocardial biopsy specimen, over an almost 2½-year period encompassing more than 1,000 biopsy specimens.

Material and Methods

Between July 1986 and October 1989, 89 adults (67 men and 22 women) between 29 and 64 years of age underwent orthotopic heart transplantation at the University of Michigan Medical Center. These patients underwent periodic serial right heart catheterization and endomyocardial biopsy for histologic monitoring of rejection after transplantation.

The hemodynamic measurements obtained at the time of catheterization included right atrial pressure, pulmonary arterial pressures, pulmonary capillary wedge pressure, and cardiac output. Cardiac output was determined by thermodilution in all patients. Heart rate and systemic blood pressure were obtained at the time of cardiac output measurement.

Simultaneous with the determination of the hemodynamic variables, right heart endomyocardial biopsy was performed under fluoroscopic guidance in all patients. Three endomyocardial specimens were taken from the right ventricle for histologic examination. One thousand, one hundred thirteen biopsy specimens were obtained immediately after right heart catheterization. The histologic specimens were graded according to a modification of the criteria of Billingham [5] as follows: grade 0 = no histologic signs of rejection or only occasional endocardial or perivascular lymphocytes; grade 1 = interstitial lymphocytic infiltrates but no myonecrosis ("mild rejection"); grade 2 = interstitial lymphocytic infiltrates and one or two isolated microfoci or myonecrosis ("focal

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moderate rejection''); grade 3 = interstitial lymphocytic infiltrates and multiple foci of myonecrosis (''moderate rejection''); and grade 4 = interstitial lymphocytic infiltrates and multiple large, perhaps confluent areas of myonecrosis, sometimes associated with focal hemorrhage, edema, and polymorphonuclear infiltrates (''severe rejection'').

Patients with rejection grade 0 or 1 received no additional treatment. Patients with grade 2 rejection underwent maximization of their chronic oral immunosuppressive therapy and early (3 to 4 week) repeat endomyocardial biopsy and right heart catheterization. Patients with the diagnosis of grade 3 rejection underwent treatment with methylprednisolone (1 g/day intravenously for 3 days) followed by repeat endomyocardial biopsy in 2 weeks. If rejection did not resolve to grade 2 or less, the patients received a 10-day course of intravenous antilymphocyte globulin therapy. Patients with a diagnosis of grade 4 rejection were hospitalized and underwent intensive treatment with steroids and either antilymphocyte globulin or OKT3 (Ortho) monoclonal antibody infusion. Repeat endomyocardial biopsy was performed 2 weeks after the initial diagnosis and subsequent treatment.

Hemodynamic data and histologic grades of rejection were correlated by analysis of variance, as well as Student's *t* test where appropriate. Correlation coefficients and regression analysis were also performed. Significance was accepted at the 95% confidence limit.

Results

There were ten deaths among these 89 patients for an overall survival rate of 89%. There were no deaths primarily caused by cardiac rejection. Three deaths were caused by pneumonia (cytomegalovirus, *Legionella*, and *Pneumocystis*). The remaining deaths were due to Guillain-Barré syndrome, metastatic pituitary tumor, suspected anaphylactic reaction to medications, intracranial bleeding, pancreatitis, and hepatitis.

Histologic Diagnosis of Rejection

The relative proportion of patients in each biopsy grade is shown in Figure 1. During the course of this study, these patients underwent 371 biopsies, which were considered as separate patient episodes. One hundred fifty-three patients had biopsy specimens read as rejection grade 0 whereas 31 patients had specimens that were rejection grade 1. These patients (184/371, 50%) with no or only mild rejection required no further treatment for rejection. Seventy-five patients (75/371, 20%) were diagnosed as grade 2 rejection (focal moderate), and these patients underwent maximization of their chronic immunosuppressive therapy with early repeat endomyocardial biopsy. One hundred three patients (103/371, 28%) had grade 3 rejection and received outpatient intravenous bolus steroid therapy [6] followed by repeat biopsy; if their condition remained unimproved, antilymphocyte globulin or OKT3 therapy was added. Nine patients (9/371, 2%) were in grade 4, and those patients required hospitalization for intensive treatment with either antilymphocyte globulin or OKT3, followed by early repeat biopsy. Five of these patients (5/9, 55%) with grade 4 rejection were symptomatic of transplant heart dysfunction at the time of their biopsy, demonstrated by shortness of breath, fatigue, and other clinical signs of congestive heart failure. Symptomatic patients with grade 4 rejection were compared with asymptomatic patients with rejection grade 4 in an attempt to identify significant differences in their hemodynamic profiles.

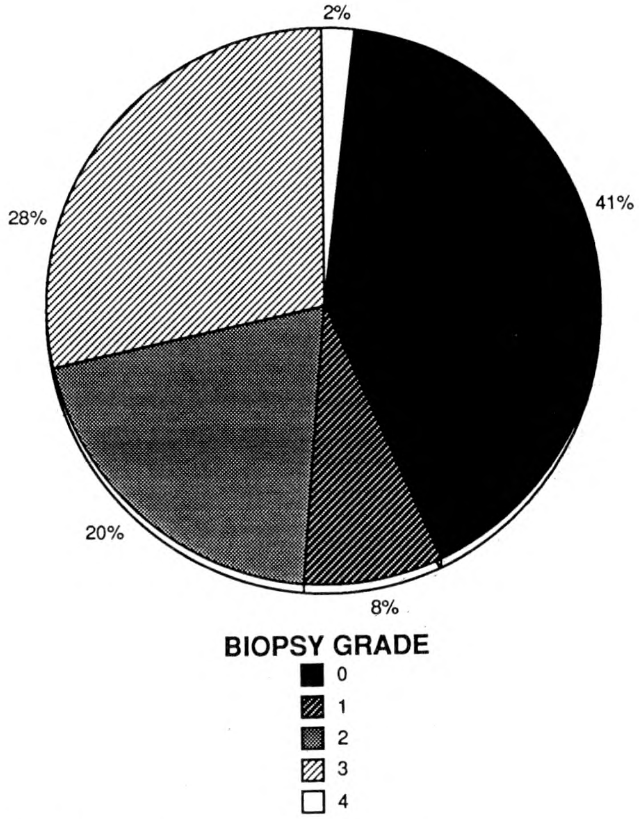

Fig 1. Percentage of patients in each biopsy grade.

Hemodynamic Data

The hemodynamic data for all grades of rejection are represented in Table 1. There were no significant differences noted with regard to hemodynamics in patients with rejection grades of 0, 1, 2, 3, or 4 when heart rate, systemic systolic or diastolic blood pressure, intracardiac pressures (pulmonary artery systolic or diastolic pressure, pulmonary capillary wedge pressure, central venous pressure), or cardiac outputs were examined. Regression analysis and correlation coefficients were all nonsignificant between all possible combinations of groups.

Although no hemodynamic variable predicted rejection, symptomatic patients with grade 4 (severe) rejection had significantly worse hemodynamics. Patients with grade 4 rejection were divided into two groups, either with or without symptoms of heart failure. No differences were noted in any intracardiac filling pressure, but cardiac output was significantly different between the two groups, with the mean cardiac output being 5.2 L/min in

Table 1. Hemodynamics Versus Biopsy Grade[a]

Variable	Biopsy Grade 0	1	2	3	4	p Value[b]
HR (beats/min)	82 ± 3	83 ± 7	77 ± 5	77 ± 4	97 ± 2	NS
BP$_s$ (mm Hg)	104 ± 5	106 ± 11	93 ± 7	97 ± 6	129 ± 7	NS
BP$_d$ (mm Hg)	66 ± 3	68 ± 7	57 ± 5	62 ± 4	80 ± 4	NS
PA$_s$ (mm Hg)	24 ± 1	23 ± 2	21 ± 3	24 ± 2	23 ± 3	NS
PA$_d$ (mm Hg)	12 ± 1	12 ± 1	12 ± 1	12 ± 1	13 ± 2	NS
PCW (mm Hg)	12 ± 1	11 ± 1	11 ± 1	12 ± 1	13 ± 2	NS
CVP (mm Hg)	8 ± 0.5	8 ± 1	8 ± 1	9 ± 1	9 ± 2	NS
CO (L/min)	5.2 ± 0.1	5.5 ± 0.3	5.2 ± 0.2	5.2 ± 0.2	4.6 ± 0.4	NS

[a] All values shown as mean ± standard error of the mean. [b] By analysis of variance.

BP$_d$ = diastolic blood pressure; BP$_s$ = systolic blood pressure; CO = cardiac output; CVP = central venous pressure; HR = heart rate; NS = not significant; PA$_d$ = pulmonary artery diastolic pressure; PA$_s$ = pulmonary artery systolic pressure; PCW = pulmonary capillary wedge pressure.

asymptomatic grade 4 patients versus 2.9 L/min in those grade 4 patients with symptoms of heart failure ($p < 0.05$).

Comment

This study demonstrates that hemodynamics as measured by right heart catheterization immediately after endomyocardial biopsy do not significantly change during rejection episodes and are not predictive or correlative of rejection in patients with endomyocardial biopsy grades of 0 through 4.

These findings confirm those of Frist and associates [7], who described the long-term hemodynamic results in patients treated with cyclosporine after orthotopic cardiac transplantation. In that study, patients undergoing chronic immunosuppression with cyclosporine had their hemodynamics determined. Their left ventricular ejection fractions, cardiac indices, and stroke work indices were essentially normal, whereas left ventricular end-diastolic pressure, mean aortic pressure, and stroke work index were increased. The transplanted hearts demonstrated no deterioration in function, despite 2.2 rejection episodes per patient in the first year after transplantation.

In a second study Greenberg and co-workers [8] described the long-term hemodynamic results in 19 patients treated with cyclosporine and prednisone undergoing endomyocardial biopsy 13 months after cardiac transplantation. Eighteen of these 19 patients were asymptomatic, but some evidence of postoperative hypertension had developed in all of them. One of 19 patients was dyspneic secondary to an opportunistic pneumonia from *Pneumocystis* and cytomegalovirus.

The hemodynamics in these transplanted patients were compared with those of 18 normal patients without cardiovascular disease. An elevated arterial pressure was noted in 56% and an elevated left ventricular end-diastolic pressure in 30% of the patients who had undergone transplantation. However, there was no significant difference in overall cardiac function between the two groups.

The endomyocardial biopsy specimens obtained in Greenberg's study were correlated with the presence or absence of fibrosis or inflammation. More than half of the patients had normal biopsy results and the remainder only had minimal to mild abnormalities. An abnormal endomyocardial biopsy, defined as fibrosis and inflammation, was noted only in 1 of 18 patients. No patient had myocardial muscle necrosis and no patient required treatment for rejection on the basis of these biopsies. The major histological changes in these patients were therefore grade 0 and 1, by the Billingham grading scale. Ten patients had had two or fewer episodes of rejection and 8 had three or more episodes of rejection since the time of their transplantation. Importantly, no relationship was shown between any inflammation or fibrosis on the endomyocardial biopsy and hemodynamic changes. The hemodynamic sequelae of chronic immunosuppression or severe rejection versus serial endomyocardial biopsies over longer periods of time were not addressed in this study.

In a further study [9] radionuclide ejection fractions were determined both early and late postoperatively in 16 patients after cardiac transplantation who were treated with standard steroid and azathioprine immunosuppression. There was no relationship between the severity of histologically evident rejection, duration of rejection, or the amount of immunosuppression required to treat rejection and the radionuclide-determined ejection fractions. In this group, mean exercise ejection fraction was 0.72. It was believed from this study that radionuclide-determined ejection fraction was not predictive of rejection and that cardiac function does not deteriorate with rejection.

Many other markers of hemodynamic function have been used in an attempt to obtain a reliable noninvasive indicator of cardiac rejection. Diastolic function [10], ventricular volumes [11], and echocardiographic-determined contractility indices [12] have all been used with varying results. Furthermore, serum and urinary markers [13], cytoimmunologic monitoring of lymphocyte subsets [14, 15], electrocardiographic analysis [16, 17], and nuclear magnetic resonance imaging [18] have also been used with variable results in an attempt to monitor rejection, guide the timing of endomyocardial biopsy, and assess the response to immunosuppressive treatment. However, no study has conclusively shown any correlation between hemodynamics and endomyocardial findings or been able to predict any hemodynamic change with the endomyocardial findings during rejection after cardiac transplantation.

Some authors [8, 19] have postulated that the decreased myocardial edema seen in cyclosporine-treated hearts has led to better hemodynamic stability despite severe rejection. Approximately half of our patients with severe (grade 4) rejection had no symptoms of transplant heart hemodynamic deterioration. Their functional status, symptomatology, and physical examination gave no clue to the severity of their rejection. However, those patients who were symptomatic of heart failure underwent urgent endomyocardial biopsy for histological analysis and predictably were found to have severe (grade 4) rejection if there was not another reason for their decompensation. In these patients, the cardiac output was worse than in those patients without symptoms who also had grade 4 rejection. Although the cardiac dysfunction noted in these symptomatic patients might be postulated to have been related to severe edema, as well as to muscle necrosis and inflammatory changes noted on biopsy, these biopsy findings were not conclusively different than those seen in the asymptomatic grade 4 patients.

Transplanted heart hemodynamics as determined by right heart catheterization do not reflect the underlying histologic changes of rejection in the transplanted heart. Right heart catheterization cannot be used as a criterion for determining rejection after cardiac transplantation as the grade of rejection does not manifest itself as proportional hemodynamic dysfunction. Although hemodynamics may be valuable for long-term surveillance in individual patients, symptoms of hemodynamic dysfunction should alert the clinician to the need for immediate endomyocardial biopsy to exclude or confirm severe rejection. Routine serial endomyocardial biopsies remain the gold standard for the diagnosis of graft rejection in all patients after cardiac transplantation.

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Delayed Chest Wall Pain Due to Sternal Wire Sutures

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This report describes 18 patients with disabling chest wall pain due to one or more sternal wire sutures. The pain occurred from 2 to 84 months after a median sternotomy. The pain was described either as sharp and stabbing or as a deep-seated ache. The involved wires had an exaggerated fibrous tissue reaction surrounding the twisted portion. The adjacent noninvolved wires had minimal reaction. In the last 7 patients, serial sections of the fibrous tissue revealed entrapment of one or more sensory nerve fibers. In 6 of the 7 electrical potentials were measured and found to be elevated, indicating wire damage during twisting. Ferroxyl tests confirmed the collection of iron ions at this anodic point as a result of corrosion. Removal of the involved wires and the fibrous tissue surrounding this anodic point relieved the symptoms of pain and tenderness resulting from entrapped sensory nerves.

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Anterior chest wall pain that continues or arises weeks after a median sternotomy is usually attributed to incisional trauma, anxiety, or nonspecific musculoskeletal problems. A recent report has described a group of patients thought to have scar-entrapped neuromas causing a neuralgic-type pain that responded to multiple nerve blocks or neurolysis [1]. Others have suggested the pain is due to a hypersensitivity reaction to the nickel contained in stainless steel [2].

In most patients, however, in the absence of a specific cause, analgesics, nonsteroidal antiinflammatory agents, heat, or some form of exercise are prescribed [3, 4].

During the past 18 years we have encountered 18 patients in whom delayed chest wall pain after median sternotomy was due to corrosion of one or more sternal wires used to reapproximate the sternum. The recognition of this cause for pain is important, especially after coronary artery bypass operations, as the pain may be confused with recurrent myocardial ischemia due to graft failure. The purpose of this paper is to present 18 patients who had disabling chest wall pain after median sternotomy in which local inflammation and fibrosis occurred around the twisted portion of the wires.

Material and Methods

Between 1972 and 1990, 18 patients were seen at the Veterans Administration Medical Center, the University of Tennessee Bowld Hospital, and Methodist Hospital in Memphis, TN, and the US Naval Hospital, San Diego, CA, with disabling anterior chest wall pain due to sternal wires used to reapproximate the sternum after median sternotomy. Sixteen patients were men and 2 were women, ranging in age from 31 to 70 years (mean age, 55.5 years). Sixteen had coronary bypass operations and 2 were explored for hemorrhage after gunshot or stab wounds of the heart.

The pain occurred from 2 to 84 months (average, 21.2 months) after a median sternotomy. It was described either as sharp and stabbing or as an ill-defined, deep-seated ache with tenderness over the twisted portion of the wire. The pain was accentuated by pressure over the involved portion of the wire or any movement of the upper extremities that resulted in increased stretch tension of the tissues overlying the anterior chest wall. It was occasionally described as radiating laterally to the adjacent chest wall, particularly if pressure was applied over the involved wire. Pain that radiated into the neck or anterior shoulder area was associated with involvement of the upper sternal wires and was accentuated by upward motion of the arms.

Before operation, each patient had a physical examination of the sternal area, consisting of palpation of each individual wire for pain or tenderness, posteroanterior and lateral chest roentgenograms, electrocardiogram, and routine laboratory studies. Six patients in this group were suspected of having myocardial ischemia as the cause for the pain. These 6 underwent several tests, which included electrocardiogram, exercise stress test, echocardiogram, and Holter monitoring.

In the 18 patients, a total of 64 wires were removed. There were 34 wires removed from areas that were tender to palpation and 30 from areas that were not tender.

In the last 6 patients studied, the electrical potential of all the wires removed, from both painful and nonpainful areas, was measured and compared with that of two pieces of unused type 316 stainless steel wire. The volt potential, measured in millivolts, was obtained by using a Corning Model 125 pH meter and a modified Corning

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Standard pH electrode. The electrode modification consisted of removing the electrode capsule and fixing alligator clamps to each electrode wire.

The twisted portion of each removed sternal wire was attached to one electrode (anode) and the remainder of the wire, which had been separated, was attached to the other electrode (cathode). The severed portions of the wire were folded in such a manner that the cut ends were not immersed in the conductive solution (normal saline solution). Each measurement was done in fresh electrolyte solution.

A ferroxyl test [5] was done on the wires removed from the last 6 patients in this series. This method employs a pH calorimetric indicator to demonstrate in vitro ionization and polarization in a corrosive cell. The test solution for the corrosive cell consisted of 10% potassium ferricyanide in 3% saline solution in agar. In the test, potassium ferricyanide will react with ionized iron at an anode to form a deep blue precipitate, Prussian blue ($Fe_4[Fe(CN)_6]_3$). The twisted portion of the wire (anode) was immersed and separated from the nontwisted portion (cathode) in the conductive solution and exposed for a period of 1 week.

A deep blue deposit on the twisted portion of the wire would indicate intense ionization of iron caused by corrosion resulting from damage of the protective chromic oxide coat. The chromic oxide coat is responsible for the corrosion resistance of type 316 stainless steel wire.

Histological studies were done on the fibrous reactive tissue found surrounding the twisted portion of the wires in the last 7 patients studied. Tissue was serially sectioned and stained with hematoxylin and eosin and S-100 immunoperoxidase.

Results

In each of the 18 patients, removal of the wires and the adjacent scar tissue resulted in complete relief from the pain and tenderness.

The sternal wires in areas that were tender to palpation exhibited a thick fibrous tissue reaction that surrounded the twisted portion of the wires (Fig 1). Adjacent wires from nontender areas exhibited very little fibrous reaction. Serial sections of the fibrous tissue surrounding the wires causing pain revealed one or more sensory nerve fibers entrapped in scar tissue (Fig 2).

Electrical potential measurements of the wires that caused pain ranged from 63 to 410 mV (mean, 200 mV); the range in the wires not associated with pain or tenderness measured from 5 to 30 mV. The electrical potential between two pieces of unused type 316 stainless steel wire measured less than 10 mV. Ferroxyl testing of the wires with increased electrical potential showed a deep blue discoloration located on the twisted portion of the sternal wire, indicating ionization of iron at this anodic point (Fig 3). The higher the electrical potential, the greater the blue deposit. The ferroxyl test was negative in all wires removed that were not associated with pain and tenderness.

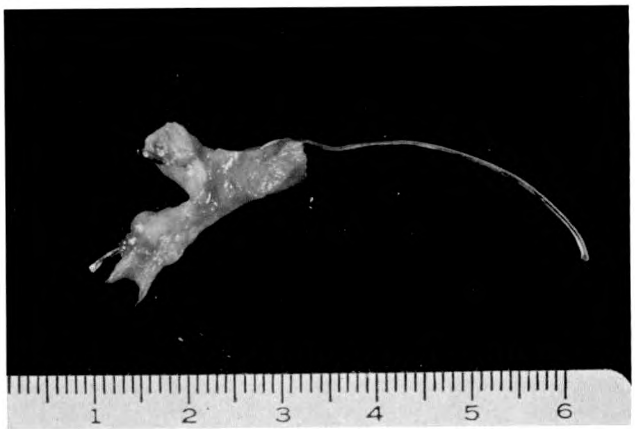

Fig 1. Exaggerated fibrous reaction at the anodic (twisted portion) area of a 316 stainless steel wire used to reapproximate the sternum.

Comment

With the introduction of stainless steel wire in the 1930s, it was thought that the inflammatory reaction secondary to electochemical corrosion and direct chemical attack would be eliminated. Although stainless steel wires are generally well tolerated in body fluids, there are occasions when corrosion does occur [6, 7].

Stainless steel is a general term covering a large number of alloys, all of which have an iron base. Steel, roughly speaking, is a solution of carbon and iron. Resistance to corrosion may be achieved by adding various elements, each of which confers specific properties on the iron. The first and most important of these elements is chromium. The remainder of the elements in 316 stainless steel wire are nickel and molybdenum [8]. The addition of molybdenum to such steel further increases the resistance to corrosion in the presence of chloride ions and organic acids that occur in body fluids.

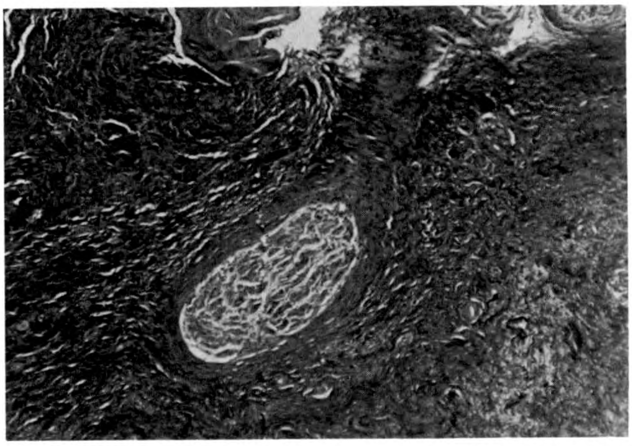

Fig 2. Hematoxylin and eosin–stained section through exaggerated fibrous reaction surrounding the anodic area of a 316 stainless steel wire, demonstrating an entrapped sensory nerve. S-100 immunoperoxidase stain confirmed this to be nerve tissue. (×125 before 50% reduction).

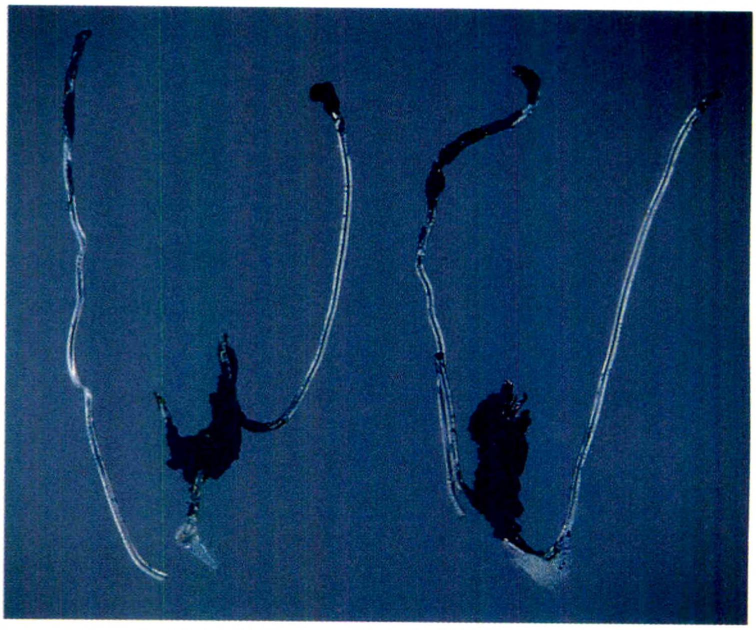

Fig 3. Ionization of 316 stainless steel wire cerclage after 1 week in a 10% solution of potassium ferricyanide and 3% saline solution in agar. The deep blue on the twisted area indicates intense ionization of iron caused by stretch damage to the oxide coat and structural damage secondary to severe twisting. Note inactivity on the majority of the rest of the wire. The blue areas at the cut ends represent iron transfer from the cutting tool and damage to the oxide coat.

The resistance of stainless steel to corrosion depends upon the presence of a thin, invisible, but continuous film of chromium oxide measuring approximately 10^{-5} mm in thickness that covers the surface and insulates the metal from corrosive electrolytes contained in body fluids [9, 10]. In normal circumstances, this protective film is self-sealing (11). If, at any point in the placement of the wire, the protective chromic oxide coat is damaged to the extent that self-sealing cannot occur, this area becomes anodic to the rest of the wire and a simple voltaic cell results. In body fluids, an electric current will flow from the anodic (damaged) portion to the cathodic (undamaged) portion of the wire.

In regard to the flow of positive electricity, the area from which the current flows into the electrolyte solution (body fluid) suffers electrolytic dissolution or corrosion. The area of the undamaged wire, into which the current flows from the electrolyte solution, receives a deposition of hydrogen ions or metal ions. If oxygen is present on the cathode, it will combine with the discharged hydrogen ions to form water [10]. In tissue iron ions will accumulate in the area adjacent to the anode, stimulating an inflammatory response.

Damage to stainless steel wire may occur during placement, as a result of severe cold working (twisting), or by rough handling of the wire with instruments. Ideally, the instruments used to grasp or to cut the wire should be made of the same metal as the implant or be lined with tungsten carbide to prevent or reduce metal transfer. Fragments of different metals, when transferred to the implanted wire, will become anodic to the implant and a corrosive cell will be established [8].

With an appreciable degree of corrosion, metal particles of disintegration will accumulate in the tissue adjacent to the anode. The tissue responds not only to the degree and rate of corrosion, but to the specific tissue toxicity of the corrosive products. Accordingly, the reaction may vary from a minimal investment of the anodic area with fibrous tissue to various degrees of fibrosis in an attempt to wall off the irritant. The fibrous investment in these patients was found surrounding the twisted portion of the wire. The greater the measured electrical potential, the greater the speed of corrosion, and the greater the fibrous reaction. Because stainless steel is an iron alloy, iron ions are expected to accumulate around the anodic portion of the wire; this may be demonstrated by subjecting the wire to the calorimetric ferroxyl test. It is the iron ions that evoke the inflammatory reaction and the fibrosis. During the process of fibrosis, sensory nerves may become entrapped in the fibrous tissue, resulting in an entrapment neuropathy.

The pain resulting from entrapment neuropathy may at times evoke concern of graft failure or inadequate revascularization in the patient who has had coronary bypass and result in further costly cardiac studies. When nerve entrapment is suspected as the cause of pain, the diagnosis may be confirmed by physical examination of the sternal area. The areas overlying the involved wires are tender to palpation and, with pressure, the pain complaints will be reproduced.

Treatment consists of removal of the wires and the adjacent scar tissue that surrounds the twisted portion. This relieves the symptoms of pain and tenderness resulting from the sensory nerve entrapment.

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Notice to Readers of *The Annals of Thoracic Surgery*

Dr Richard M. Peters, who has functioned as an Associate Editor in charge of book reviews for the past 11 years, at his request retired from this position at the time of the Interim Meeting of The Society of Thoracic Surgeons in Chicago, September 21, 1990. He will remain as an Editorial Board member. Dr Peters has performed a great service for the readers of *The Annals*, and we are grateful to him.

Dr J. Kent Trinkle has agreed to be the new Associate Editor in charge of book reviews. Any correspondence concerning this section of *The Annals* should be sent directly to him at the address listed below:

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Comparison of Supraannular and Subannular Pledgeted Sutures in Mitral Valve Replacement

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Ten fresh canine hearts were used to compare the peak left ventricular pressure required to disrupt prosthetic mitral valves sutured in place with horizontal mattress sutures with either subannular or supraannular pledgets. Each group consisted of 5 animals. A 29-mm Medtronic mitral valve was secured in the mitral position with ten pledgeted sutures. The aorta was cannulated and normal saline solution was infused into the left ventricle until valvar disruption occurred. The peak pressure and the location and mechanism of disruption were then noted. At the peak left ventricular pressure required for valvar disruption, no individual sutures were broken. Instead, in all specimens a subannular myocardial rupture occurred in the posterior portion of the mitral annulus along the extent of the atrioventricular groove. In addition, the posterior wall of the left atrium dissected upward subsequently. Significantly greater pressures were required in the group with subannular suture placement as compared with the supraannular group (354 ± 37 versus 236 ± 33 mm Hg; $p < 0.0007$). These data suggest that placement of horizontal mattress sutures with pledgets in the subannular position is superior to the currently recommended method of supraannular suture placement in mechanical valves.

(Ann Thorac Surg 1991;51:60–4)

Cardiac surgeons have long debated the issue of the preferred suture technique for securing a mitral valve replacement. It is obvious that one would prefer to implant the valve so as to reduce the incidence of atrioventricular separation and yet permit free and unimpinged valve leaflet mobility. Several clinical series have examined suture technique in relation to mitral valve replacement, but there has been no consensus as to the superiority of one technique [1, 2]. Stiles and associates [3] examined four suture techniques in the porcine heart. They found that prosthetic valves sewn in place with horizontal mattress sutures and pledgets in the supraannular position had the greatest holding strength. However, these workers did not examine the difference between supraannular and subannular placement of the pledgets.

Newton and associates [4] compared simple interrupted, figure-of-8, supraannular, and subannular pledgeted sutures for securing a prosthetic mitral valve. With their experimental model, they were able to demonstrate that horizontal mattress sutures with subannular pledgets had superior holding potential. However, in both Stiles' and Newton's studies the direction of the force used to cause disruption was opposite to the native forces applied to a mitral prosthesis in a functioning heart. Therefore, we have examined the two most frequently used techniques in such a way that the forces applied are in the same direction as the forces in the heart, so that the recommendation by many valve manufacturers that supraannular placement of the sutures affords the best stability could be definitively supported or refuted. In addition, the location and possible mechanism of prosthetic valve disruption are considered.

Material and Methods

Adult mongrel dogs (average weight, 22 kg) were chosen as the experimental model because of the physiological and structural similarity of the canine heart to that of the human. Each group consisted of 5 animals. The dogs were killed with sodium pentobarbital and the chest was entered through a median sternotomy. The arrested heart and great vessels (average weight, 234 g) were immediately excised en bloc and maintained in a 1,000-mL plastic beaker containing 20 to 30 mL of normal saline solution at room temperature. The mitral valve was exposed through an atriotomy in the posterior aspect of the left atrium and the annulus was prepared by removal of both leaflets, leaving a 1.5- to 2-mm rim of valvar tissue. The annulus was then sized using mitral valve sizers and, overall, a 29-mm valve was found to be the most appropriate size. To eliminate the 10% native regurgitant factor of prosthetic valves, a 29-mm Medtronic mitral valve was completely sealed with medical-grade silicon before it was secured in the mitral position. The suture material was 2-0 braided polyester (Mersilene; Ethicon, Inc) with rb-1 tapered needles and 3 × 6-mm firm Teflon felt pledgets. Ten interrupted horizontal mattress sutures were then placed at approximately 2- to 3-mm intervals around the annulus. The effects of ischemia and cell necrosis were negated by completion of the entire procedure and experiment within approximately 90 minutes.

In the group with the supraannular pledgets, tissue bites were taken from the atrial side down through the

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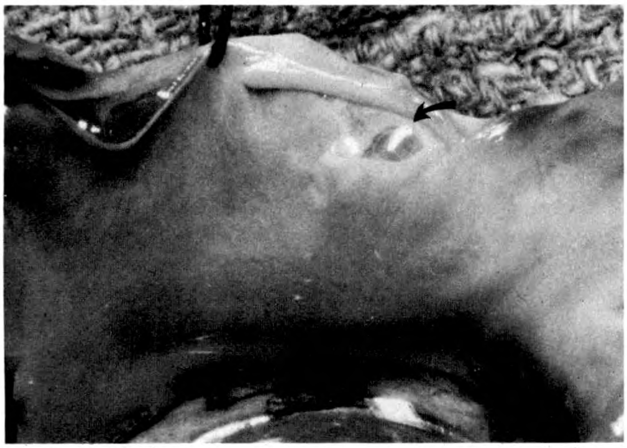

Fig 1. Arrow *indicates subannular myocardial rupture.*

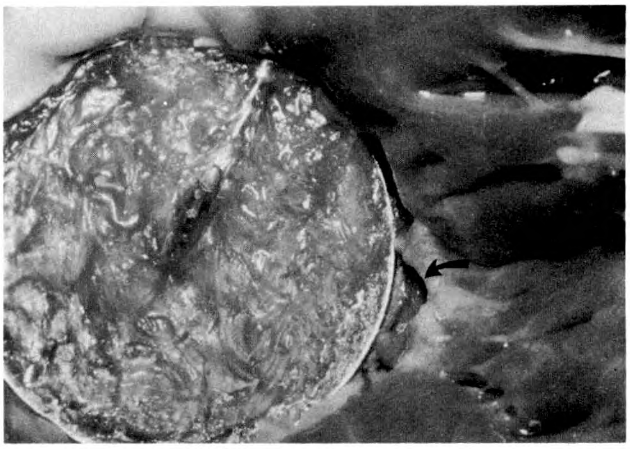

Fig 2. Arrow *indicates dilatation of the posterior wall of the left atrium resulting from subsequent dissection after myocardial rupture.*

annulus to include 2 to 3 mm of annulus in the bite. Sutures were then passed upward through the valve sewing ring, creating an eversion of annular tissue and sewing ring. Maintaining the same depth of suture placement as in the supraannular group, sutures in the subannular group were placed from the ventricular side upward through the annulus and then through the sewing ring such that a sandwich of pledget, annulus, and sewing ring was constructed.

A 20F cannula was then inserted across the aortic valve and secured with umbilical tape around the base of the aorta. A roller pump infused normal saline solution so that a ramp pressure from 0 mm Hg to bursting pressure was created over an average time span of 30 seconds. Pressures were recorded using a Cobe force-displacement transducer coupled to a Grass model 7 polygraph.

The left ventricular pressure at which myocardial rupture occurred, as indicated by a rapid fall in ventricular pressure, was used as the experimental end point. Statistical significance between the mean disruptive pressures of the two groups was determined using a two-tailed Student's t test. Anatomical features of the disruptions were also analyzed.

Results

The location of the myocardial rupture was the same in every trial. The posterior portion of the mitral annulus was the site of separation regardless of supraannular or subannular suture placement. In Figure 1 is shown the subannular myocardial rupture in the area of the atrioventricular groove. There was also a dissection beginning at the myocardial rupture and progressing superiorly in the posterior wall of the left atrium in all animals (Fig 2).

The pressures required to disrupt the mitral prostheses were remarkably reproducible in each group. Individual pressure measurements for each trial are shown in Table 1, and Figure 3 is a representative example of a left ventricular pressure tracing in the subannular group. The myocardial tears occurred at significantly greater pressures in the subannular group as compared with the supraannular group (354 ± 37 versus 236 ± 33 mm Hg; $p < 0.0007$) (Fig 4).

Comment

Many factors contribute to the successful implantation of a mitral prosthesis. Left ventricular disruption has been attributed to aggressive debridement of the mitral annulus, trauma to the papillary muscle, needle puncture of the atrioventricular groove, and still other causes [5]. In the present study we examined suture techniques that have been examined experimentally in only two previous studies [3, 4].

The data from this study corroborate the finding of Newton and co-workers [4] that horizontal mattress sutures with pledgets placed in the subannular position provide the greatest stability for mitral prostheses. In addition, the pressures required to cause myocardial rupture, when the sutures are placed in the supraannular position, are within the range of left ventricular pressures possible in the postoperative period for patients undergoing a cardiac procedure. On the other hand, the pressures seen in the subannular group are rarely if ever seen in the clinical setting, thus lending additional support to the argument for the superiority of subannular pledgeted suture placement.

Table 1. Individual Pressure Measurements (mm Hg) for Each Trial

Trial No.	Subannular Pledgets	Supraannular Pledgets
1	350	200
2	370	260
3	300	200
4	350	260
5	400	260
Mean ± SD	354 ± 36.5	236 ± 32.9

SD = standard deviation of the mean.

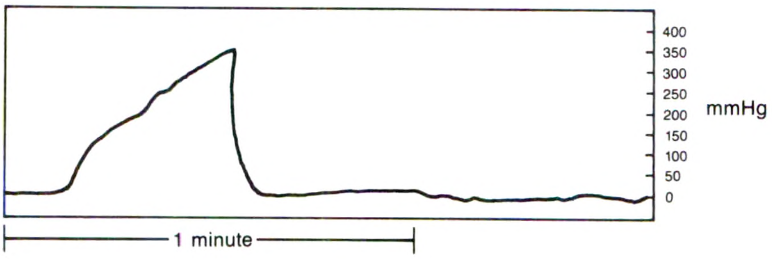

Fig 3. Representative example of a left ventricular ramp pressure from 0 mm Hg to a rupture pressure of 350 mm Hg in an animal in the subannular group.

We also observed that the posterior portion of the annulus was consistently the area involved in rupture of the myocardium. Vincente and associates [6], in an anecdotal report of a type I ventricular injury after mitral valve replacement, described the atrioventricular groove as the weak area of the mitral annulus owing to the fact that the mitral annulus is only in continuity with the endocardium of the left atrium and there is no muscular continuity between atrium and ventricle. This could explain the subannular myocardial rupture and dissection up the posterior wall of the left atrium in all trials in the present study. In the clinical setting, it would seem that a subannular rupture and subsequent dissection in the posterior atrial wall is a very real threat, particularly in an early postoperative dehiscence associated with an elevation of left ventricular pressure.

We have speculated on a possible mechanism to explain the superiority of the subannular technique over the supraannular method of suture placement. Figure 5 shows a schematic representation of the supraannular technique and the subsequent effects of gradual increases in left ventricular pressure. Note that when the pledgets are placed in the supraannular position, an eversion of annular tissue and sewing ring is created. Therefore, when the pressure is increased, the annular tissue is torqued in such a way that only one portion is contributing to the holding strength of the annulus. This is represented in the figure by point *b'*, which is providing the holding strength, while point *a'* is made slack and thus is not contributing to the security of the mitral prosthesis. Figure 6 shows horizontal mattress sutures with pledgets placed in the subannular position. With this suture technique a sandwich of pledget, annulus, and sewing ring is created such that both points *c'* and *d'* are contributing to the holding strength of the mitral annulus, thereby increasing the stability of the mitral prosthesis subjected to either increasing left ventricular pressures or possibly even the forces of normal left ventricular pressure over time.

It is obvious that differences may exist between normal canine and pathologically altered human annular tissue. Such differences might include severe calcific mitral stenosis or redo mitral valves. However, canine mitral valve tissue is very delicate, and thus may be an acceptable model for such circumstances in which the annular tissue is very friable and the surgeon is concerned about the holding strength of the mitral annulus.

Translation of these results to the clinical situation requires further qualification and correlation with clinical experience. Factors related to the maximum stress that occurs during left ventricular contraction were not tested in this in vitro model. Additionally, atrioventricular separation usually occurs during periods of hypotension

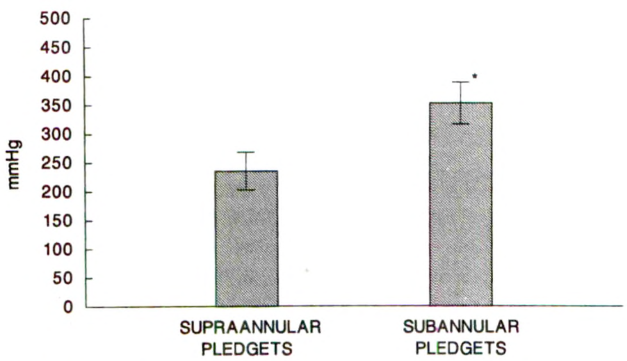

Fig 4. Mean pressures required for myocardial rupture in the supraannular versus the subannular groups. Bar indicates ± one standard deviation. The difference between the groups is significant ($p < 0.0007$).

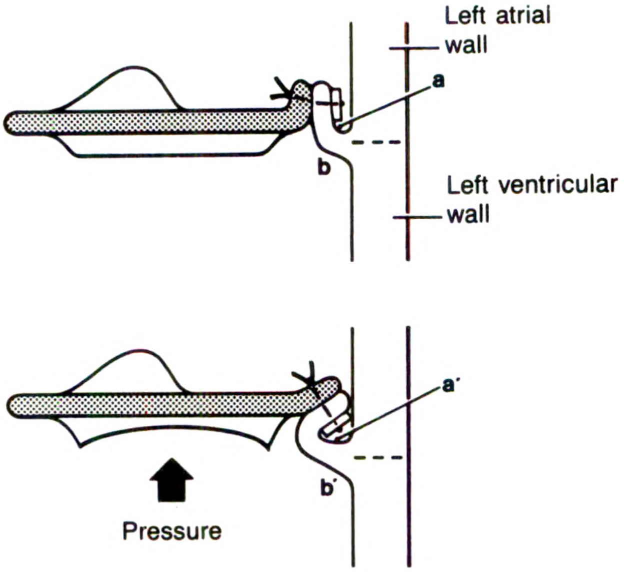

Fig 5. Schematic representation of the supraannular technique and the subsequent effects of gradually increasing left ventricular pressure. Note that point b' *is contributing to the holding strength of the annulus while point* a' *is made slack and thus is not contributing to the security of the mitral prosthesis.*

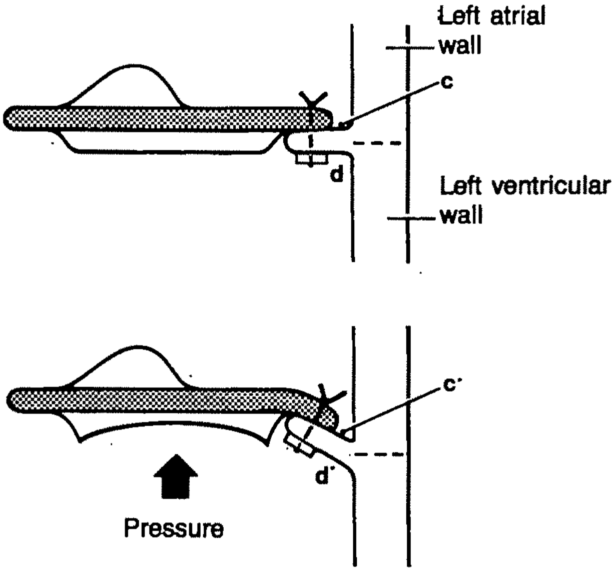

Fig 6. Schematic representation of the subannular technique and the subsequent effects of gradually increasing left ventricular pressure. Note that in comparison with the supraannular technique, both points c' and d' are contributing to the holding strength, thereby increasing the stability of the mitral prosthesis.

when the surgeon attempts to end bypass; therefore, this model does not fully explain the cause of atrioventricular separation.

It is obvious that many different factors are involved in the proper implantation of a mitral valve. Of these, the surgeon has the greatest control over the suture technique. Also, the same technique may not be mandated in every mitral valve operation. Yet in those situations in which the integrity of the annulus is in doubt and one is concerned about the possibility of a myocardial rupture, our present evidence would suggest, based on our own clinical experience and our data presented here, that one consider placement of horizontal mattress sutures with the pledgets in the subannular position.

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INVITED COMMENTARY

Left ventricular rupture is a dreadful complication of mitral valve replacement. Fortunately it has been practically eliminated by preservation of the posterior mitral valve apparatus during operation. Although unproven, this would imply a causal relationship of resection of the posterior mitral valve apparatus and left ventricular rupture. In the present article, Chambers and Heath attempt to add to the already voluminous but inconclusive literature as to the etiology of this condition. They do so in an in vitro heart preparation in which different techniques of suturing of the mitral valve (subannular and supraannular mattress sutures) are used. The left ventricle is then distended by pressure until rupture occurs. The superiority of subannular suture placement is clearly demonstrated in terms of left ventricular rupture. Some points need to be discussed. First, it is unfortunate that another series of experiments in which the mitral valve apparatus was either preserved or cut followed by valve replacement was not carried out, as it might have shed more light onto the important question as to the role of the mitral valve apparatus in this condition.

Second, contraction of the heart would probably change the force alignment of the atrioventricular walls in contradistinction to the flaccid heart that was used in this study. However, if we follow with the theory that Chambers and Heath propose, cardiac contraction in fact would probably increase the tension on the ventricular side of the wall with supraannular pledgeted sutures and perhaps increase the incidence of disruption. On the other hand, the pressures would probably be more evenly distributed in the subannular position, as Chambers and Heath also have suggested.

Third, preservation of the chordae tendinae of the mitral valve apparatus, which has been shown to be effective in the preservation of left ventricular function, may also play an important role in decreasing the incidence of atrioventricular disruption and providing more even distribution of forces in the atrial and ventricular walls. In fact, preservation of the mitral valve apparatus would act to decrease the tension on the ventricular side of the atrioventricular tension barrier, as suggested by Chambers and Heath. By a decrease in this tension, we believe the incidence of disruption would be decreased and the pressure at which disruption occurs would be increased. This obviously should be addressed and would be an excellent addition to any future research in this area. It is noteworthy that the literature has shown a reduction in atrioventricular wall separation with preservation of the mitral valve apparatus during operation.

Finally, the normal heart is different from the diseased heart in terms of the amount of pressure required for left ventricular disruption. A calcified annulus, which is often encountered in rheumatic valvular disease, may also change the results and conclusions of Chambers and Heath in the clinical setting. Calcification of the annulus with the distribution of forces suggested by Chambers and Heath would more likely cause dehiscence of the mitral valve apparatus rather than disruption.

Overall, this paper deserves merit for its simplicity and originality. It suggests that, in clinical situations in which it is not possible to preserve the mitral valve apparatus and in which mechanical valves are used, subannular placement of pledgeted sutures is probably safer.

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Staged Repair of Pulmonary Atresia With Ventricular Septal Defect and Major Systemic to Pulmonary Artery Collaterals

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Fifty-eight consecutive patients with pulmonary atresia, ventricular septal defect, hypoplastic pulmonary arteries with arborization defects, and major aortopulmonary collaterals were entered into a program for staged surgical repair between January 1979 and July 1989. Prerepair preparatory procedures were designed to (1) encourage native pulmonary artery growth by increasing blood flow and (2) unifocalize pulmonary blood supply by transplanting or ligating major collaterals. A total of 121 staging procedures were performed with an overall mortality of 10.3%. One hundred thirty-four major collaterals were either ligated or transplanted. Thirty patients eventually underwent hemodynamic repair with an early mortality of 3.3% and late mortality of 10.0%. Twenty-six current survivors of repair remain clinically well after a mean follow-up of 3.6 years. Ten patients are currently in various stages of preparation. Twelve patients (20.7%) failed to achieve minimum requirements for repair after staging and await further palliation or heart-lung transplantation. The principles of management have evolved over the years and are discussed.

(Ann Thorac Surg 1991;51:65–72)

Patients with pulmonary atresia and ventricular septal defect (VSD) are not suitable for one-stage repair when the pulmonary arteries are hypoplastic and have severe arborization defects and when sizeable portions of the lungs are supplied by major systemic to pulmonary collateral arteries (MAPCAs) [1]. These patients have long been managed with palliative shunt procedures [2] or palliative gusset repair [3] of the right ventricular outflow tract. Experience with systemic to pulmonary shunts in tetralogy of Fallot has revealed that hypoplastic pulmonary arteries can be induced to grow by increasing blood flow in them [4, 5]. Hemodynamic repair of pulmonary atresia and VSD, hypoplastic pulmonary arteries, and MAPCAs could be envisaged provided that the pulmonary arteries could be encouraged to grow by preparatory shunt procedures and that the multiple sources of pulmonary blood supply could be centralized to a single pulmonary arterial system. Major aortopulmonary collateral supply to the lungs is complex [6, 7]. Although some are the only source of blood supply to an area of lung, others may overlap with branches of the native pulmonary artery, and others still may feed directly into central pulmonary arteries. Many MAPCAs exhibit areas of stenosis outside or within the lung parenchyma [8] and when not stenotic are prone to develop changes of hypertensive vascular disease as a function of time. "Unifocalization" of pulmonary blood supply involves transplantation or ligation of these MAPCAs [9]. Precise angiographic delineation of the various sources of pulmonary blood supply is therefore an essential prerequisite to the staged surgical management of this condition.

For editorial comment, see page 8.

At the Royal Children's Hospital, Melbourne, a program for the staged repair of this condition has evolved over the years. Initially operation was aimed only at palliation and consisted of placement of a right ventricular outflow tract (RVOT) gusset. Subsequently the form of initial palliation was altered to enhance the possibility of eventual repair and evolved from peripheral systemic–pulmonary shunts to central aorta–pulmonary shunts. Currently, surgical management is usually staged as follows:

1. Midline sternotomy and central aorta to pulmonary artery shunt.
2. Bilateral thoracotomies and transplantation or ligation of MAPCAs.
3. Repeat sternotomy, closure of VSD, and insertion of a valved conduit between the RVOT and the reconstructed pulmonary arteries.

A total of 58 patients have so far entered this program, and this report details our experience with this group of patients.

Patients and Methods

Between January 1979 and July 1989, 58 patients with a diagnosis of pulmonary atresia and VSD, severely hypoplastic pulmonary arteries with clinically significant arborization defects, and MAPCAs were accepted into a program for staged repair. Fifty-three patients were seen

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Table 1. Age Distribution at Entry Into Program

Age (y)	No. of patients
<2	28
2–5	10
5–10	8
10–20	6
>20	6

primarily in this hospital whereas the remaining 5 had palliative procedures performed in other hospitals and were entered into the program upon subsequent referral. There were 33 male and 25 female patients ranging in age from 1 day to 39 years (median age, 2 years 6 months). Age distribution at first operation is detailed in Table 1. Four patients were seen in infancy with severe cyanosis and underwent initial palliation as an emergency. The remaining 54 patients were clinically stable with varying degrees of cyanosis and effort intolerance at entry. Except for 3 neonates who underwent emergency shunt procedures after echocardiographic evaluation, all patients underwent cardiac catheterization and angiography before the initial operation. In 2 patients the initial procedure was an exploratory sternotomy in an effort to locate central pulmonary arteries that were not identifiable on detailed angiography. In a third patient with additional severe aortic regurgitation, the first operation was an aortic valve replacement. A fourth patient had excessive pulmonary blood flow through MAPCAs and underwent isolated MAPCA transplantation as the initial procedure. In the remaining patients, the initial operation was designed to increase blood flow through the native pulmonary arteries.

A total of 191 cardiac catheterizations with angiography were performed in the 58 patients to assess intracardiac and extracardiac anatomy and hemodynamics. All MAPCAs were identified by selective injections and their course and distribution defined as clearly as possible. This often required multiple studies. The native pulmonary arteries were defined by retrograde filling from a MAPCA injection (when a communication between them existed), by injection across a surgically created systemic–pulmonary shunt when present, or by retrograde pulmonary venous wedge injections. Hemodynamic data were obtained with the patients paralyzed and on intermittent positive-pressure ventilation with an inspired oxygen concentration of 30%. Pulmonary to systemic blood flow ratios were calculated from the oximetry data using standard formulas. Angiograms were analyzed for the total number of MAPCAs in each patient, their distribution, and presence of stenoses. Native pulmonary arteries were scrutinized for presence of arborization defects. Pulmonary artery diameters were recorded at the hilum and predicted postrepair right ventricle to left ventricle pressure ratio (pRV/LV) was calculated using the Birmingham formula [10]: $pRV/LV = 0.484\ [Dia.RPA/Dia.AO + Dia.LPA/Dia.AO] + 0.2007$, where AO = aorta, Dia = diameter, LPA = left pulmonary artery, and RPA = right pulmonary artery.

The various surgical procedures performed were as follows:

Procedures Aimed at Encouraging Native Pulmonary Artery Growth

RIGHT VENTRICULAR OUTFLOW TRACT PATCH. This was performed in 6 patients in the early part of the program. The procedure was performed using cardiopulmonary bypass, moderate hypothermia, and cardioplegic arrest. The main pulmonary artery was incised longitudinally and the incision carried across the pulmonary annulus into the right ventricular infundibulum. Pulmonary valve tissue, if present, and obstructing subvalvar myocardium were resected and right ventricular to pulmonary artery continuity was established with autologous pericardium in 5 patients and low-porosity Dacron in 1. Major aortopulmonary collaterals feeding directly into the pulmonary arterial system were ligated simultaneously in 3 patients. This procedure was subsequently abandoned in favor of systemic to pulmonary shunts.

PERIPHERAL SYSTEMIC TO PULMONARY SHUNT. Classic or modified Blalock-Taussig shunts were performed in 20 patients as the initial procedure. We have preferred a modified Blalock-Taussig shunt using a thin-walled Gore-Tex interposition graft, as it involves less dissection and causes less distortion of the pulmonary arteries. Three of these patients subsequently needed a second shunt on the contralateral side and 2 others needed a central shunt. Four patients had peripheral shunts performed after a prior central shunt or RVOT patch. In 3 patients a Gore-Tex graft was interposed between the ascending aorta and either pulmonary artery. Peripheral shunt procedures also provided an opportunity for simultaneous MAPCA operation whenever indicated. Selection of peripheral Gore-Tex shunt sizes was similar to our selection in other patients requiring shunts. For children weighing more than 2.5 kg and up to about 5 years of age a 5-mm shunt was used. A 6-mm shunt was occasionally used in larger children and an 8-mm shunt was used in 1 adult-sized patient.

CENTRAL ASCENDING AORTA TO MAIN PULMONARY ARTERY SHUNT. A central aorta to main pulmonary artery shunt is currently our procedure of choice for enhancement of pulmonary artery growth in patients with very small confluent pulmonary arteries and has been performed in 28 patients as an initial procedure. The procedure was usually performed through a midline sternotomy. However, when all left chest MAPCAs required ligation, both these procedures were done simultaneously through a left thoracotomy. Whenever a tapering main pulmonary artery segment was present it was detached from the right ventricular outflow tract and anastomosed end-to-side to the left of the ascending aorta as far posteriorly as possible to avoid tension on the right pulmonary artery. When the main and branch pulmonary arteries were intermediate in size a short segment of Gore-Tex graft was interposed between the ascending aorta and pulmonary artery bifurcation (6 patients) as a means of avoiding excessive flow. In general, for central Gore-Tex shunts we use a size smaller than we would use for a peripheral shunt.

MAPCA Ligation/Transplantation

A total of 66 MAPCAs were ligated in 32 patients. Major aortopulmonary collaterals were ligated when they clearly duplicated supply from the native pulmonary arteries; they were also ligated when they demonstrated wide anatomical communications with the native pulmonary arteries. Major aortopulmonary collaterals that supplied less than one bronchopulmonary segment and were too small to be transplanted were also ligated. Sixty-eight other MAPCAs were transplanted in 34 patients. Major aortopulmonary collaterals were considered suitable for transplantation if they (1) supplied more than one bronchopulmonary segment independently of the central pulmonary artery, (2) had no peripheral stenosis, or (3) were not hypertensive. In a few instances, MAPCAs were transplanted even when they overlapped areas of supply with the central pulmonary artery as it was believed that transplantation would increase the net pulmonary vascular bed and thereby decrease pulmonary vascular resistance. Operation on MAPCAs was performed through right or left thoracotomies in all except 5 patients, in whom MAPCAs were ligated through a midsternotomy at the time of RVOT patching (3 patients) or hemodynamic repair (2 patients). Major aortopulmonary collaterals requiring ligation were isolated as close as possible to the site of origin from the aorta or its major branches and doubly ligated with silk suture. In the event of doubt regarding feasibility of ligation, the MAPCA was initially temporarily snared. If there was no blanching of the appropriate lung segment and if systemic saturations did not fall substantially then the MAPCA was permanently ligated.

Major aortopulmonary collaterals requiring transplantation were gently occluded with vascular clamps and detached from their systemic inflow. The ends were then beveled and the MAPCAs anastomosed end-to-side to the branch pulmonary artery using a continuous 7-0 polypropylene suture. The anastomosis was made as long and as oblique as possible to provide the largest possible anastomotic lumen. When more than one MAPCA required transplantation, the largest one was initially anastomosed to the pulmonary artery and the others were then anastomosed end-to-side to this MAPCA. In some patients the siting of the anastomosis also served the purpose of relieving pulmonary artery stenosis. When direct anastomosis was not feasible owing to inadequate length of the MAPCA, as was often seen with MAPCAs arising from the lower descending thoracic aorta, a Gore-Tex graft was interposed (8 patients). More recently in 4 patients a segment of azygos vein was used as an interposition graft to transplant a MAPCA from a right descending thoracic aorta to the right pulmonary artery [11].

Table 2. Types of Conduit Used for Right Ventricle to Pulmonary Artery Connection

Type of Conduit	No. of Patients
Homograft conduit[a]	8
Tascon valved conduit[b]	8
Hancock valved conduit[c]	8
Ionescu-Shiley valved conduit[d]	2
Polystan valved conduit[e]	1
St. Jude Medical valve[f]	3

[a] Pulmonary or aortic processed and preserved in liquid nitrogen (O'Brien's method). [b] Knitted Dacron graft containing freehand-mounted porcine aortic valve and rendered low porosity by impregnation with collagen. [c] Woven, low-porosity Dacron graft containing freehand-mounted porcine aortic valve. [d] Woven low-porosity Dacron graft containing "in-line" stent-mounted bovine pericardial valve. [e] Noncrimped porous Dacron tube lined by tanned pericardium and containing freehand-mounted pericardial valve. [f] Inserted within a previously placed right ventricular outflow patch.

Hemodynamic Repair

Patients were considered suitable for hemodynamic repair when (1) calculated pRV/LV ratio by the Birmingham formula was less than 0.7, using pulmonary artery diameters at the hilum allowing that stenoses proximal to this point could be surgically relieved, (2) no sizeable MAPCAs remained, (3) more than two thirds of the lung segments were connected to the native pulmonary arteries, and (4) there was a net left to right shunt. Thirty patients eventually underwent hemodynamic repair. In 2 patients repair was undertaken as a semiurgent procedure owing to excessive pulmonary flow and ventilator dependence after a central shunt. In a third patient a growing false aneurysm of the central shunt secondary to bacterial endocarditis necessitated emergency repair.

Repair was performed through a midline sternotomy using cardiopulmonary bypass and moderate hypothermia. Preexisting shunts were ligated and the VSD was closed with a Dacron patch through a right ventriculotomy under cardioplegic arrest. Right ventricular outflow reconstruction was then performed on a beating heart. Autologous or bovine pericardium was used to enlarge the branch pulmonary arteries, often well into the hilum. Right ventricular to pulmonary artery continuity was then established using a valved conduit. The types of conduits used are listed in Table 2. In 3 patients in whom a prior RVOT patch had been placed a prosthetic valve was incorporated into the right ventricular outflow tract.

Results

A total of 121 staging procedures were performed in 58 patients. There were six deaths during this phase, a mortality of 10.3% (70% confidence limits, 6.2% to 16.2%) for staging alone. Two of the deaths were early, one in an acidotic neonate who remained acidotic after an emergency central shunt into markedly hypoplastic pulmonary arteries and another in a 25-year-old patient, 1 week after a modified Blalock-Taussig shunt, from bronchopneumo-

Table 3. Comparison of Age at Entry Into Program and Eventual Outcome

Clinical Outcome	Age at Entry (y)				
	<2	2–5	5–10	10–20	>20
Complete repair (n = 30)	15 (1)[a] [1][b]	8 (0) [1]	5	1	1
Death during staging (n = 6)	3 (1) [2]	0	1 [1]	0	2 (1) [1]
Unfit for repair (n = 12)	2	2	2	4	2
Awaiting repair (n = 10)	8	0	0	1	1
Total	28	10	8	6	6

[a] Numbers in parentheses are early deaths. [b] Numbers in brackets are late deaths.

nia and pulmonary hemorrhage. There were four late deaths. A 31-year-old patient with cardiomegaly, recurrent atrial arrhythmias, moderate aortic valve incompetence, and congestive heart failure died of progressive congestive heart failure and renal failure 3 months after a peripheral shunt and MAPCA transplantation. A 2-year-old boy died after a mesenteric artery embolus 4 months after a fourth preparatory operation that consisted of an open mitral valvotomy and valvoplasty for congenital mitral stenosis. A 2-year-old girl died of progressive congestive heart failure 2 months after a central shunt and did not report to the hospital early enough. The fourth patient, a 9-year-old boy, died suddenly, presumably from an arrhythmia, 15 months after placement of an RVOT patch. This last patient was well suited for repair but had suffered a serious cerebrovascular accident after interim catheterization study and was withdrawn from further operation by the parents.

Of the 52 survivors, 12 patients are presently considered unsuitable candidates for a hemodynamic repair after having undergone a total of 21 staging procedures. Two of these patients had complete absence of central pulmonary arteries and were not offered any further operation after initial exploratory sternotomies. They remain alive though deeply cyanosed 4 years and 8 years after operation. A third patient had central pulmonary arteries measuring only 1 mm in diameter and remains severely cyanosed after a Gore-Tex shunt into a left lung collateral. In 3 patients, the left pulmonary artery was absent. None of them had MAPCAs to the left lung that were suitable for possible unifocalization. Two remain well palliated after shunts to the right pulmonary artery and a third has crippling cyanosis and awaits a heart-lung transplant.

Five other patients are considered unsuitable for repair because of inadequate pulmonary artery growth after initial shunting procedures. All of them remain well palliated and will be considered only for further palliative operation or heart-lung transplantation if and when further cyanosis develops.

The last patient in this group was taken up for hemodynamic repair after three preparatory procedures. At operation, however, the pulmonary arteries were found to be smaller than expected and only a right ventricle to pulmonary artery valved conduit was placed, the VSD being left open. He continues to have marked cyanosis and effort intolerance.

Ten patients continue in various stages of the program. They have undergone a total of 20 preparatory procedures. It is presently considered that they will be suitable candidates for repair eventually.

Thirty patients have undergone hemodynamic repair. This group of patients constitute the subject of the subsequent report.

Clinical Profile

There were 17 male and 13 female patients ranging in age from 1 month to 34 years (median age, 1 year 10 months) at first operation. Twenty-three were less than 5 years of age at entry; 5 were between 5 and 10 years of age, and only 2 were older than 10 years (Table 3).

Nineteen patients had confluent hypoplastic central pulmonary arteries on initial evaluation. In one patient no central pulmonary arteries could be demonstrated; however, both lungs were well supplied by large MAPCAs. All patients had at least two major aortopulmonary collaterals.

Only 1 patient in this group had critical cyanosis in infancy requiring an emergency shunt operation at 1 day of age. A total of 71 preparatory operations were required (average, 2.3/patient) before hemodynamic repair. These comprised 20 sternotomies and 53 thoracotomies. The initial operation performed was an RVOT patch in 4, peripheral systemic to pulmonary artery shunt in 10, and a central shunt in 16 (using Gore-Tex in 5) (Table 4). Three patients with an initial modified Blalock-Taussig shunt required a contralateral modified Blalock-Taussig shunt, and 2 others had an additional central shunt performed.

Fifty-eight MAPCAs were ligated and 57 others trans-

Table 4. Outcome of Initial Procedure to Augment Native Pulmonary Artery Flow

Clinical Outcome	Initial Procedure (54 patients)		
	RVOT Patch	Peripheral Shunt	Central Shunt
Complete repair	4 (0)[a] [1][b]	10 (1) [1]	16 (0) [1]
Intercurrent death	1 (0) [1]	2 (1) [1]	3 (1) [2]
Unsuitable for repair	0	6	3
Awaiting repair	1	2	6
Total	6	20	28

[a] Numbers in parentheses are early deaths. [b] Numbers in brackets are late deaths.

RVOT = right ventricular outflow tract.

planted. Five patients required Gore-Tex grafts for MAPCA transplantation, and in 3 others an azygos vein graft was used. The average number of MAPCAs transplanted or ligated per patient was 3.8.

Median age at repair was 4 years 2 months (range, 3 months to 35 years). Median interval between entry into the program and completion was 2 years 8 months (range, 15 days to 7½ years).

Predicted pRV/LV ratios calculated by the Birmingham formula from angiograms decreased from 0.9 (range, 0.51 to 1.35) at entry to 0.51 (range, 0.41 to 0.71). Mean pulmonary blood flow expressed as ratio of pulmonary to systemic blood flow increased from 1.7:1 (range, 0.6:1 to 3:1) to 2.3:1 (range 1:1 to 4:1) before hemodynamic repair. Mean prestaging hemoglobin level was 162 g/L (range, 104 to 200 g/L) and decreased to a mean of 141 g/L (range, 109 to 199 g/L) before repair.

Hemodynamic repair was performed on an elective basis in 26 patients. In 4 patients repair was precipitated due to excessive pulmonary blood flow and ventilator dependence in 2, mycotic pseudoaneurysm of the central shunt with impending rupture in 1, and accidental wire coil embolization of the left pulmonary artery during attempted embolization of a large MAPCA in the fourth patient.

The results of hemodynamic repair were as follows:

MORTALITY. There was one early death (early mortality, 3.3%; 70% confidence limits, 0.4% to 10.9%) 3 weeks after repair as a result of *Candida* septicemia and pancreatitis leading to multiorgan failure. This patient had an otherwise satisfactory repair with an intraoperative pRV/LV ratio of 0.3.

There have been three late deaths (late mortality, 10%; 70% confidence limits, 4.4% to 19%). One was a sudden death in a 13-year-old girl 2 years after repair, presumably due to an arrhythmia. Cardiac catheterization 18 months after repair had confirmed an excellent hemodynamic repair with a pRV/LV of 0.4. Autopsy did not reveal any structural cardiac defect to explain her death.

In the other 2 patients repair had been unsatisfactory. Both had pRV/LV ratios in excess of 1, requiring fenestration of the VSD patch 9 days and 1 month after repair, respectively. The first patient had tracheomalacia in addition, remained in respiratory failure and ventilator dependent, and had treatment withdrawn at the parents' request 3 months after repair. The second patient remained cyanotic and clinically unwell after fenestration of her VSD patch and died of progressive heart failure 2 years 3 months after repair. An autopsy was refused.

FOLLOW-UP. Twenty-six current survivors of repair have been followed up from 1 month to 7 years (mean, 3.6 years). All remain clinically well, with no cyanosis. Twenty-four are in New York Heart Association class I and 2 have class II symptoms.

Seventeen of the survivors have had at least one postoperative hemodynamic study and angiography at an interval of 1 month to 88 months (mean, 30 months) after repair. The pRV/LV ratio at last study was less than 0.5 in 12 patients, and these are considered to have an excellent repair. Figure 1 shows illustrative angiograms from 1 of these patients. In 1 patient the pRV/LV ratio was 1.2 at first study owing to a large residual VSD. The VSD was closed satisfactorily at reoperation and at subsequent study the ratio had dropped to 0.39.

In 5 patients the pRV/LV ratio was more than 0.5 (range, 0.7 to 0.9). In 2 patients the elevated pressures are attributed to stenosis at the origin of the branch pulmonary arteries. Both underwent balloon dilations unsuccessfully. They remain clinically well, however, and it is planned that the stenoses would be relieved surgically at the time of conduit replacement, which will eventually be necessary. In a third patient elevated right ventricular pressures are accounted for by a combination of small residual VSDs (systemic to pulmonary shunt ratio = 1.5:1), stenosis of the origin of left pulmonary artery, and hypertensive vascular disease of the right lung resulting from a previous large-flow shunt. A 34-year-old patient has a postrepair pRV/LV ratio of 0.9 as a result of an occluded left lower lobe pulmonary artery and multiple peripheral stenoses in the other branches. Successful balloon dilation of some of these stenoses have not dropped the right ventricular pressure and it is likely that he has clinically significant occlusive pulmonary vascular disease. The fifth patient has a pRV/LV ratio of 0.7 but has no pulmonary artery stenosis, residual VSD, or arborization defect; this patient presumably has mild occlusive pulmonary vascular disease.

Three patients have residual arborization defects involving at least one lobar segment each. In 2 of these, however, the pRV/LV ratio is less than 0.5.

Clinically significant residual MAPCAs were present in 4 patients and successfully embolized in 3. Six other patients underwent attempts at balloon dilation of branch pulmonary artery stenoses with successful relief in only 1.

Nine survivors await postoperative catheterization. They remain clinically well on no antifailure medication. All have undergone routine cross-sectional echocardiography, which has not revealed any clinically significant residual VSD or right ventricular outflow gradient in any. It is expected that cardiac catheterization would reveal satisfactory hemodynamics in them.

Comment

The feasibility of surgical correction in pulmonary atresia with VSD is largely dependant on the size of the pulmonary arteries and the extent of their distribution. One-stage repair is possible when the pulmonary arteries are of adequate size and have no arborization defects; and is now performed in most centers with low operative risk [1, 12, 13]. In patients with moderate hypoplasia with minimal or no arborization defects hemodynamic repair has been achieved after prior augmentation of pulmonary artery growth with an RVOT patch [14] or systemic to pulmonary artery shunt with or without ligation of MAPCAs [15–17].

Patients with severe hypoplasia of the native pulmonary arteries with serious arborization defects and

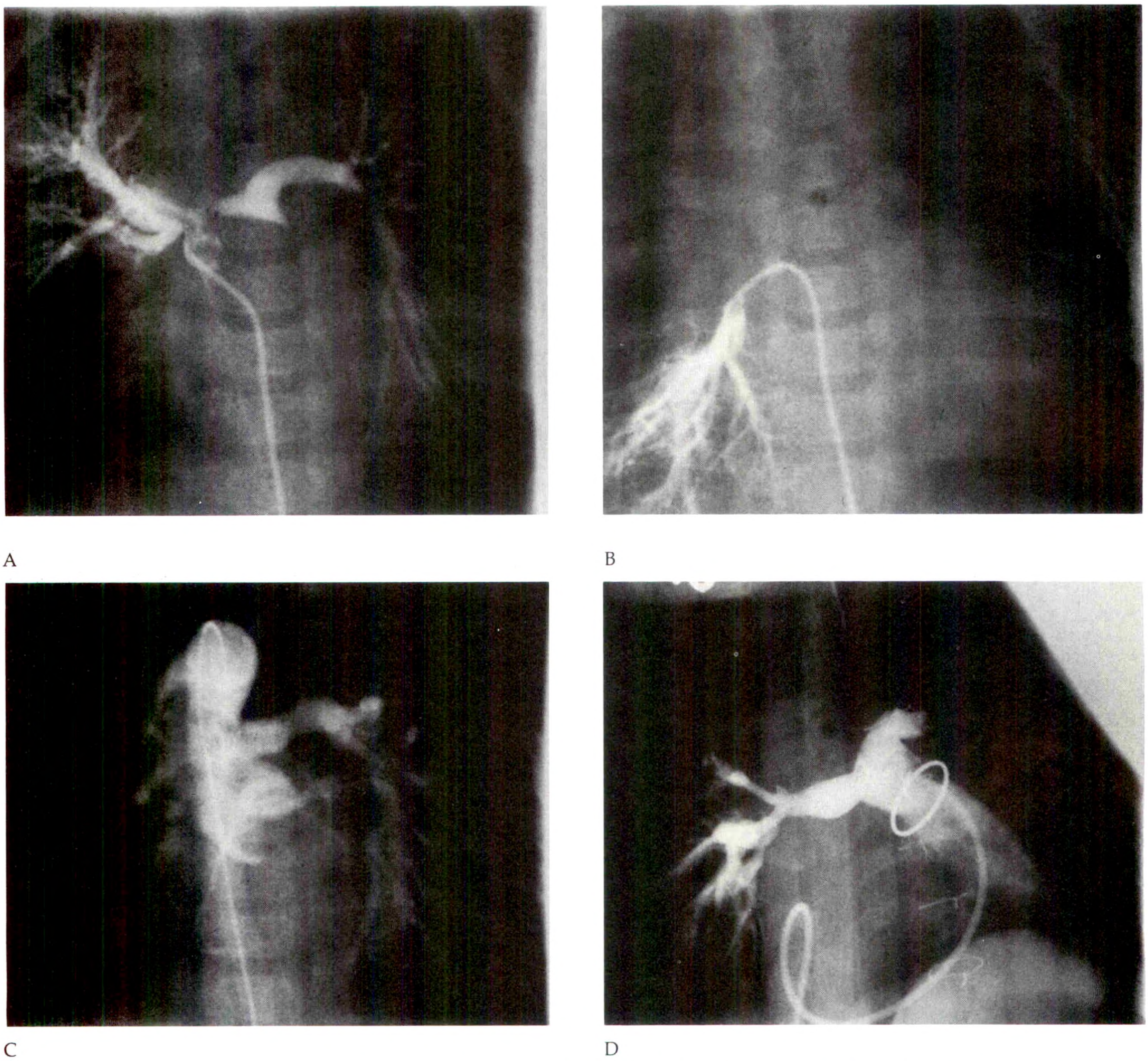

Fig 1. (A) Selective injection into major aortopulmonary collaterals (MAPCAs) arising from mid-descending thoracic aorta, supplying right upper lobe, and filling the native pulmonary arteries. Left lower lobe pulmonary artery fills faintly because of wash-out of contrast medium by blood from another MAPCA. (B) Selective injection into second MAPCA arising lower down along the descending thoracic aorta, not communicating with the native pulmonary artery. (C) Angiogram from the same patient 3 weeks after central end-to-side main pulmonary artery to aorta shunt, ligation of left lung MAPCA, and transplantation of the two MAPCAs in the right chest using azygos vein. There has been appreciable growth in the size of the pulmonary arteries. (D) Pulmonary artery angiogram of the same patient after complete repair, showing well unifocalized right lung blood supply and adequate size of right and left pulmonary arteries. Peak systolic right ventricle to left ventricle pressure ratio was 0.5.

MAPCAs constitute the most difficult end of the spectrum of pulmonary atresia and VSD and remain one of the most challenging groups of patients to manage surgically. Untreated the majority of them are destined to die early of either severe cyanosis and its attendant complications or progressive congestive cardiac failure [18]. Although surgical management has often been the logical treatment alternative it has hitherto been essentially of a palliative nature. More recently, however, the realization that hemodynamic repair may be possible after appropriate preparation has led to the concept of planned palliation with a view to maximize the chances of eventual repair. Reports of successful hemodynamic repair in this situation are few and largely limited to case reports [9, 19–22]. This report summarizes the results of our attempts at achieving hemodynamic repair in this situation in a staged manner. It needs to be emphasized, however, that no 2 patients in this group were alike in their pattern of pulmonary blood supply, and so although the basic principles of management have been adhered to, the specific treatment modalities, their timing, and their sequence have varied from patient to patient. No attempt has been made therefore to present statistical comparisons of the efficacy of the various surgical procedures, many of which need to stand the test of time. However, many lessons have been learnt from this experience and these have helped to evolve the current guidelines for the management of these patients.

Two factors are key to achieving successful repair in this situation: (1) the ability to achieve satisfactory growth of the native pulmonary arteries and (2) the ability to unifocalize all pulmonary artery blood supply to these native pulmonary arteries. Experience with systemic to pulmonary artery shunts in tetralogy of Fallot has conclusively demonstrated that small pulmonary arteries may be stimulated to grow by increasing flow through them. However, unlike tetralogy, the severity of the hypoplasia and the frequent occurrence of congenital or iatrogenic stenosis often hinder a satisfactory and even growth. The central shunt was therefore a logical evolution, in that it provides a high uniform flow through both pulmonary arteries at a substantial pressure head. We believe currently that it is the most effective procedure for stimulating growth in small pulmonary arteries. Shunt flow increases exponentially with the growth of the pulmonary arteries, and a torrential increase in pulmonary blood flow with resultant pulmonary edema or occlusive pulmonary vascular disease is an ever-present risk. These patients therefore need to be followed up closely and hemodynamic repair must be performed as soon as satisfactory pulmonary artery growth has been achieved. Rarely this may need to be done on a semiurgent basis as was necessary in 2 of our patients.

Like some other groups we have had reservations about the suitability of the RVOT patch as a means of promoting pulmonary growth, especially in severely hypoplastic pulmonary arteries [3, 23]. Though 4 of the 6 patients receiving an RVOT patch eventually underwent repair with good results in 3, this procedure was abandoned early in the series. Aneurysmal dilatation and bifurcation stenosis are frequent complications, and patch placement has the added disadvantage of requiring cardiopulmonary bypass [24]. It probably still has a role in patients with mild to moderate hypoplasia of the pulmonary arteries. The peripheral systemic to pulmonary artery shunts of any variety have in our opinion a substantial potential for producing iatrogenic stenosis of small pulmonary arteries at the anastomotic site, which results in uneven growth, is difficult to repair (particularly on the left side), and jeopardizes the prospects of future hemodynamic correction [24, 25]. The classic Blalock-Taussig shunt with its inevitable tension on a small pulmonary artery has been particularly disappointing in this respect. Currently we feel that peripheral shunts play an adjuvant role to the central shunt and are particularly useful in relieving hypoxemia resulting from transplantation of large MAPCAs.

Our experience also suggests that the younger patients are more likely to respond to attempts at accelerating pulmonary artery growth and eventual repair. Twenty-eight of 46 patients (60.8%) younger than 10 years underwent complete repair eventually whereas only 2 of the 12 patients (16.6%) older than this did so. Patients with high blood flow through MAPCAs are likely to be referred late because of absence of clinically significant cyanosis. As a result they are more likely to have patchy pulmonary vascular obstructive disease [26, 27], cardiomegaly, congestive heart failure, and later progressive aortic valve incompetence. The probability of safe progress through multiple surgical stages to hemodynamic repair is low in these patients. On the other hand older patients with low MAPCA flow because of proximal stenoses do not have cardiomegaly, retain good ventricular function, and are likely to have better results. However, the development of profuse small mediastinal collaterals (not MAPCAs) makes operation very tedious and difficult. We currently opt to commence staging at about 1 year of age.

Appropriate management of MAPCAs is the other key to success in this difficult patient group. The elegant works of Thiene, Haworth, and co-workers [7, 26, 27] have shown that MAPCAs when not connected to the native pulmonary arteries branch within the lung parenchyma into smaller branches finally ending in efficient respiratory units, in a manner similar to the native pulmonary arteries. Ligation of these collaterals would undoubtedly lead to the permanent exclusion of vital bronchopulmonary segments and reduction of effective pulmonary vascular bed, precluding definitive repair. There is also a risk of segmental infarction [1]. Transplantation of these MAPCAs therefore is logical if a well-arborized, low-resistance pulmonary artery supply is to be achieved. Major aortopulmonary collaterals feeding into the native pulmonary arteries or too small for transplantation need to be ligated to reduce the problem of excessive intracardiac return and low perfusion pressures during repair [17].

Intraoperative assessment of MAPCAs is often necessary before a decision regarding transplantation or ligation can be made as precise angiographic delineation is not always possible. Major aortopulmonary collaterals that are thin walled and under low pressure are more suitable for transplantation than those that feel tense and thick walled. Areas of stenosis may often be missed on angiograms and must be carefully looked for. Direct anastomosis is ideal; when it is not feasible the use of autologous material like azygos vein for interposition is preferable to use of prosthetic grafts, which have a high late occlusion rate [9]. An ever-present risk, however, is the development of late stenosis either at the site of anastomosis or distally within the lung parenchyma, which could jeopardize late results. An interesting observation has been the relative inability to dilate these stenoses by balloon catheter techniques postoperatively (five failures in six attempts).

Patients with nonconfluent or absent native pulmonary arteries seem to be least likely to progress to hemodynamic repair. These patients are probably best managed by hilar manifolding using bovine pericardial tubes as reported by Sawatari and associates [22] and Barbero-Marcial and colleagues [21]. We have successfully attempted this technique in only 1 patient.

The choice of conduit for the final repair has shifted from the Dacron valved conduits in the early part of the series to cryopreserved homografts in the latter half. The need for conduit change over the course of years is of course inevitable. Dacron conduits have been preferred in the smaller patients as subsequent conduit change becomes technically simpler. On the other hand the better longevity of the cryopreserved homograft makes it the more appropriate choice in the larger patient.

To conclude, therefore, surgical management in this difficult subgroup of patients is intensive. Optimal results can be obtained with careful planning based on accurate angiographic and physiologic data and execution of the surgical procedures with precision. The short-term results are encouraging and likely to improve; however, longer follow-up is required to provide the answers to foreseeable problems such as the fate of transplanted MAPCAs and the progression of pulmonary vascular obstructive disease after repair. The program is ongoing and we hope to find the solutions to many of the current problems in due course.

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Right Pulmonary Artery Obstruction After Pulmonary Artery Banding

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Serial assessment of pulmonary artery flow by Doppler echocardiography was carried out in 15 infants after pulmonary artery banding. Three infants were identified as having branch pulmonary artery obstruction based on diastolic pulmonary artery flow. It is concluded that this flow profile may be specific for branch pulmonary artery obstruction after pulmonary artery banding.

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Pulmonary artery banding is an effective palliative surgical procedure in infants with congenital heart defects associated with increased pulmonary blood flow [1, 2]. The rationale is to protect the pulmonary vasculature from irreversible obstructive pulmonary arteriopathy until such time as definitive surgical correction of the underlying cardiac lesion can be undertaken with minimal operative risk. Although a relatively simple surgical procedure, it is not without serious morbidity. Insufficient restriction of pulmonary blood flow by too loose an application of the pulmonary artery band may result in inadequate protection of the distal pulmonary vasculature. Migration or erosion of the banding material resulting in partial or complete obstruction of a branch pulmonary artery is well described [3, 4] and may seriously complicate ultimate surgical correction of the cardiac defect, potentially increasing the operative mortality and morbidity. Detection of branch pulmonary obstruction is often difficult by standard noninvasive imaging techniques. We report here Doppler echocardiographic diagnosis of proximal branch pulmonary artery obstruction after pulmonary artery banding.

Material and Methods

Fifteen infants aged 2 weeks to 8 months (mean age, 7 weeks) with cardiac lesions resulting in excessive pulmonary blood flow underwent pulmonary artery banding palliation according to previously published techniques [1]. Doppler echocardiographic interrogation of the pulmonary artery band gradient was initially carried out within 48 hours of operation and then 24 to 48 hours before hospital discharge in all infants. In addition, all infants had regular measurements of pulmonary band pressure gradients after discharge.

The maximum pulmonary band pressure gradients were obtained using color flow–directed continuous-wave Doppler (Toshiba SSH-65A) measurements from standard subcostal and parasternal orientations. Color M-mode assessment of the proximal branch pulmonary arteries was obtained from a suprasternal or high parasternal approach.

Results

All infants had adequate Doppler pulmonary artery band pressure gradients with a mean gradient of 72 ± 11 mm Hg at the time of hospital discharge. Three of the 15 infants demonstrated continuous flow in the proximal right pulmonary artery both on color M-mode (Fig 1) and continuous-wave Doppler echocardiography (Fig 2). These flow patterns were first detected at 2 weeks, 8 weeks, and 3 months after pulmonary artery banding. Branch pulmonary artery narrowing was not identified by two-dimensional real-time imaging.

Eight infants subsequently underwent cardiac catheterization. All 3 infants with Doppler-detected diastolic pulmonary artery flow demonstrated proximal right pulmonary artery obstruction by the banding material on angiography. None of the other infants had angiographic or echocardiographic evidence of branch pulmonary artery obstruction. There was no difference in the systolic pulmonary artery band gradients between those with (68 ± 5 mm Hg) and those without (74 ± 12 mm Hg) branch pulmonary artery obstruction. Figure 3 shows pulmonary angiography before and after pulmonary artery banding in an infant with diastolic right pulmonary artery flow first detected 3 months postoperatively. Stenosis of the right pulmonary artery by the banding material is evident.

On serial postoperative chest radiographs none of these infants had obvious evidence of branch pulmonary artery obstruction. One infant died after operation consisting of closure of a ventricular septal defect, removal of the pulmonary artery band, and reconstruction of the right pulmonary artery. A second child died after cardiac catheterization, having been seen initially with sudden onset of marked cyanosis. Both pulmonary angiography and autopsy findings confirmed severe narrowing of the origin of the right pulmonary artery with no obstruction of the left pulmonary artery. The other infant continues to do well 1 year after a corrective operation requiring reconstruction of the right pulmonary artery.

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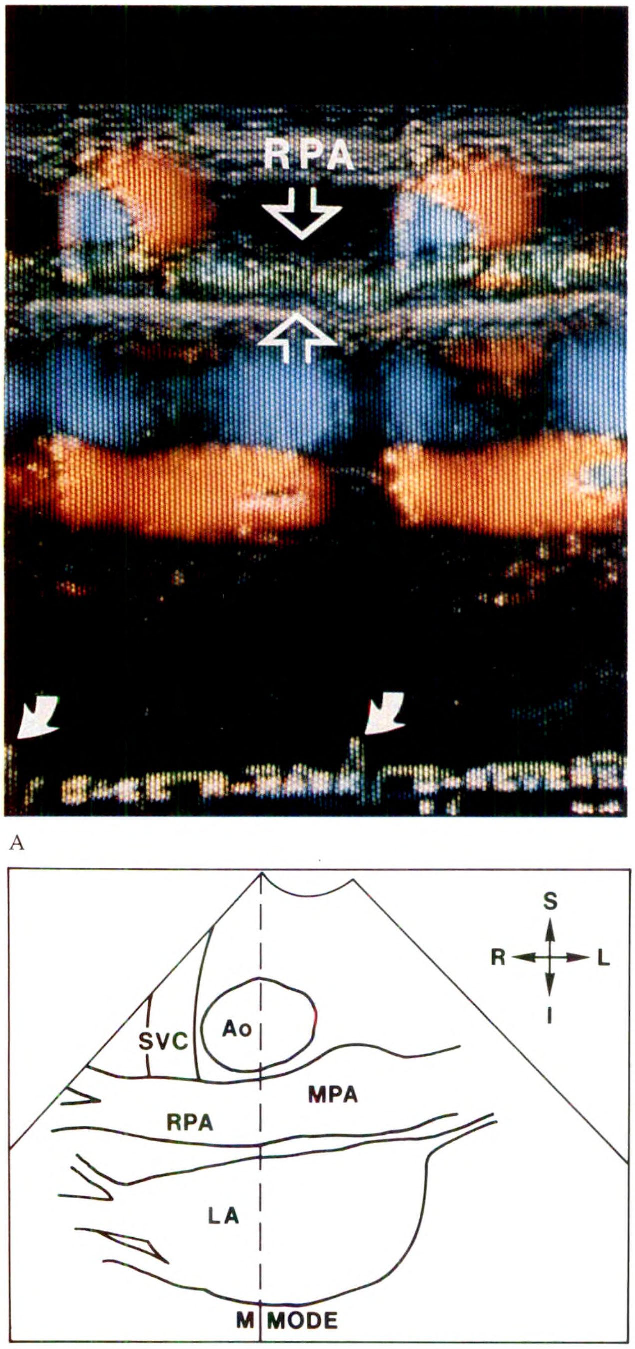

Fig 1. *(A) Suprasternal color M-mode echocardiography demonstrating diastolic right pulmonary artery flow* (open arrows*).* Closed arrows *indicate electrocardiographic R waves. (B) Schematic demonstrating orientation of color M-mode study shown in (A).* (Ao = *aorta;* LPA = *left pulmonary artery;* MPA = *main pulmonary artery;* RPA = *right pulmonary artery;* SVC = *superior vena cava.)*

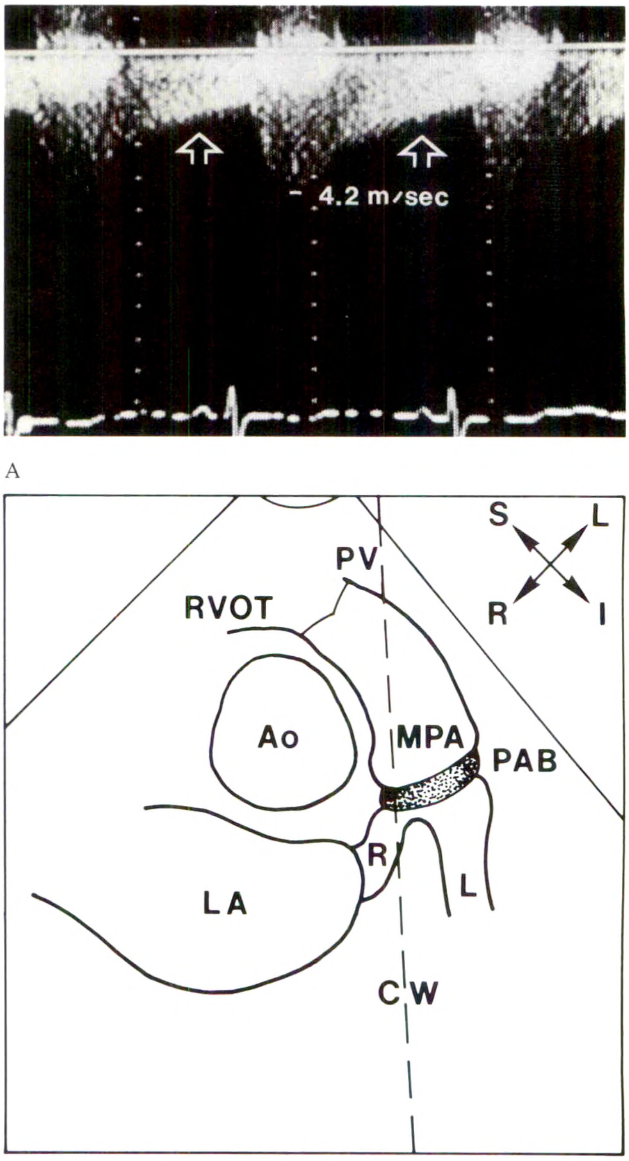

Fig 2. (A) Continuous-wave Doppler recording showing peak systolic velocity of 4.2 m/s (~70 mm Hg) across pulmonary artery band. Open arrows *indicate diastolic flow in the right pulmonary artery. (B) Schematic demonstrating orientation of continuous-wave Doppler echocardiography in (A) across the pulmonary artery band* (PAB) *and proximal right pulmonary artery.* (Ao = *aorta;* CW = *continuous wave Doppler alignment;* L = *left pulmonary artery;* MPA = *main pulmonary artery;* PV = *pulmonary valve;* R = *right pulmonary artery;* RVOT = *right ventricular outflow tract.)*

Comment

Obstruction of a branch pulmonary artery after pulmonary artery banding is well described [3]. Failure to recognize this complication potentially increases the operative mortality of subsequent corrective operations as extensive reconstruction of the involved pulmonary arterial segment may be necessary. Standard chest radiographs may not be sufficiently sensitive to detect partial unilateral pulmonary flow obstruction as evident in the cases described here.

The demonstration by Doppler echocardiography of diastolic flow in the proximal right pulmonary artery may be a specific sign of branch pulmonary artery obstruction. This flow pattern was observed only in infants with

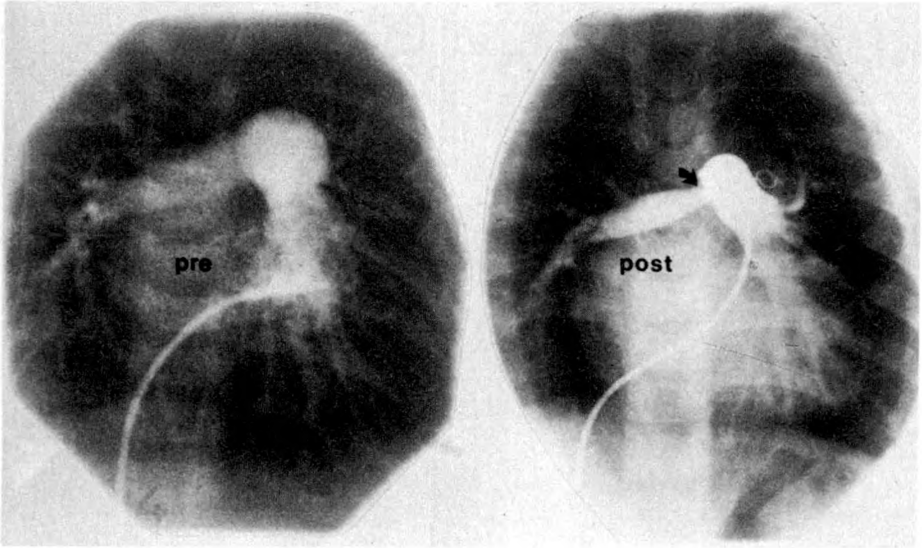

Fig 3. Frontal main pulmonary artery angiography before (pre) *and after* (post) *pulmonary artery banding demonstrating postoperative stenosis of right pulmonary artery* (curved arrow).

angiographically confirmed branch pulmonary artery obstruction. The mechanism presumably is secondary to encroachment by the pulmonary artery band on the origin of the right pulmonary artery which, in comparison with the left pulmonary artery, arises more proximally and at a more acute angle from the main pulmonary artery. This results in a persistent gradient between the main and branch pulmonary artery, thereby accounting for the continuous Doppler flow profile observed. All of the branch pulmonary artery obstructions reported here involved the right pulmonary artery; however, the small number of patients involved does not permit any conclusions to be made as to the incidence of left pulmonary artery obstruction. Right pulmonary artery obstruction occurred in the presence of an adequate pressure gradient across the pulmonary artery band.

The abnormal Doppler flow patterns were not seen in earlier postoperative studies, suggesting that branch pulmonary artery obstruction may be a progressive phenomenon. If recognized before progression to more severe forms of obstruction, it may be possible to intervene early to ultimately avoid more extensive pulmonary artery surgical reconstruction. However, this study does not address the issue of how severe branch pulmonary artery need be before abnormal diastolic flow becomes detectable by Doppler echocardiography. Low flow sensitivity of current color-flow systems may preclude earlier detection of low-velocity continuous diastolic flow associated with postoperative branch pulmonary artery obstruction. Hence, a clinically significant degree of branch pulmonary artery obstruction may be necessary before detection by Doppler techniques.

To avoid branch pulmonary artery obstruction, we now perform pulmonary artery banding using an anterior rather than a lateral thoracotomy, facilitating better visualization of the relationship of the banding material to the proximal right pulmonary artery. Our current approach is to study branch pulmonary flow by Doppler echocardiography early and serially after pulmonary artery banding. The recognition of a diastolic pulmonary artery flow pattern is an indication for pulmonary angiography and either revision of the pulmonary artery band or, when appropriate, early corrective operation.

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Altered Cellular Immune Function in the Atelectatic Lung

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Pulmonary atelectasis is common and may predispose the lung to infection. We have previously shown that atelectasis impairs alveolar macrophage antibacterial function. This study examines the effect of atelectasis on the cytotoxic function of lymphocytes harvested from the bronchoalveolar space of atelectatic lung segments by bronchoalveolar lavage. Specifically, we studied natural killer and lectin-dependent cell-mediated cytotoxicity in peripheral blood and bronchoalveolar lavage lymphocytes from the atelectatic lower lobes and contralateral normal lobes in a group of 8 dogs. We observed a decline of natural killer and lectin-dependent cell-mediated cytotoxicity to 62.7% and 61.5%, respectively, of preatelectasis control values in the affected lung lobes ($p < 0.01$). Simultaneous measurements of cytotoxic activity of bronchoalveolar lavage lymphocytes harvested from the unaffected contralateral normal lungs were comparable with control values. On the other hand, natural killer and lectin-dependent cell-mediated cytotoxicity activities in peripheral blood lymphocytes were significantly increased in animals having right lower lobe atelectasis (166.7% and 154.7% of pretreated normal control, respectively, $p < 0.01$). Atelectasis was also associated with an influx of polymorphonuclear leukocytes into the bronchoalveolar compartment. These findings confirm the presence of natural killer cells and cytotoxic lymphocytes in the bronchoalveolar compartment and demonstrate an atelectasis-induced impairment of local bronchoalveolar lymphocyte function. Such a dysfunction of local lung cellular host defenses may render the atelectatic lung susceptible to infection.

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Pulmonary atelectasis is a common pathological entity. It frequently occurs after operation and trauma or may complicate other forms of chronic or acute lung injury. It is thought to predispose the affected lung to infection [1, 2]. The mechanism of this increased susceptibility to pneumonia has not yet been fully elucidated. An alteration in local cell-mediated immune defenses has been postulated. Shennib and associates [3] demonstrated an atelectasis-induced impairment of the ability of alveolar macrophages to phagocytose opsonized bacteria in vitro. This dysfunction was found to be reversible with reexpansion of the collapsed lung segment.

Alveolar macrophages play an important role in lung cellular defenses. They clear particulate and microbial contaminants of the lower respiratory tract [4], and initiate lymphocyte-mediated immune responses by interacting with alveolar lymphocytes once they are exposed to antigens [5]. Specific and nonspecific cell-mediated and humoral immunity provided by the recruited pulmonary T and B lymphocytes are also prominent components of pulmonary defense mechanisms [6]. More recently, natural killer (NK) cell activity has been detected in bronchoalveolar mononuclear cells [7]. Natural killer cells, a subpopulation of large granular lymphocytes with spontaneous cytotoxic activity against a wide variety of target cells without prior sensitization, are thought to have an immunosurveillance role against viral infected cells, neoplasms, and fungi [8, 9]. These components of the local pulmonary cellular defenses act in concert to maintain the sterility of lung alveoli.

This study examines the effects of pulmonary atelectasis on the cytolytic function of lymphocytes harvested locally from the bronchoalveolar compartment and systemically from the circulating peripheral blood in a canine model. Specifically, we examined the nonspecific NK and lectin-dependent cell-mediated cytotoxicity (LDCMC) of lymphocytes obtained by bronchoalveolar lavage (BAL) from collapsed lung segments and contralateral unaffected lung, as well as circulating lymphocytes from peripheral blood.

Material and Methods

Induction of Lobar Atelectasis

Fully conditioned, 20- to 25-kg mongrel dogs (n = 11) were anesthetized with nembutal (30 mg/kg intravenously). Lobar atelectasis was induced by the method described by Shennib and associates [3]. In brief, a small midline neck incision was made to expose the trachea. A small lateral incision in the trachea allowed introduction of a double-lumen balloon catheter into the right lower lobe bronchus with the aid of the fiberoptic bronchoscope. The balloon was inflated with a radiopaque solution. Atelectasis was confirmed roentgenographically 30 hours after occlusion of the bronchus. The radiopaque solution

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in the balloon helped to ascertain that it stayed inflated and in good position. Atelectasis was maintained for 48 hours and the catheter was removed just before BAL of the atelectatic right lower lobe. All animals were awake and moving about during 48 hours of atelectasis.

The animals were handled and cared for in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Cell Preparation

BRONCHOALVEOLAR LAVAGE LYMPHOCYTES. Bronchoalveolar lavage of the right lower lobe was performed at least 5 days before the induction of atelectasis to obtain the baseline normal lung lymphocyte cytotoxicity and BAL cellular profile on all animals. It was then repeated 48 hours after the onset of atelectasis on both the affected right lower lobe and the unaffected left lower lobe. Briefly, aliquots of 40 mL of phosphate-buffered saline solution were injected into the selected lung segment through a sterile polyethylene tube wedged into the segmental bronchus; after a few minutes' delay to allow lavage fluid to reach the distal alveolar space, it was suctioned gently via a three-way stopcock at the other end of the tube to a suction trap. On average 300 mL of lavage fluid was injected with 60% retrieval rate. Gentle aspiration of BAL fluid was done with a narrow-tipped pipette to disperse mucus strands, and then the fluid was filtered through a loose cotton gauze to remove remaining clumps of mucus. Cells were then collected by centrifuging BAL fluid at 2,500 rpm for 10 minutes. Bronchoalveolar lavage cells were washed three times with RPMI-1640 medium enriched with 10% fetal calf serum, penicillin (100 IU/mL), streptomycin (100 μg/mL), and glutamine (2 mmol/L); this medium is hereafter referred to as RPMI-complete. Total BAL cell counts were performed manually with an improved Neubauer hemocytometer using 1% acetic acid as the counting fluid. Trypan blue dye exclusion test was routinely used to assess viability of BAL cells, which was usually more than 90%. Slide preparations were made in a cytocentrifuge using 100 μL of the BAL cell suspension (concentration, 5×10^6 cells/mL) and spinning at 500 rpm for 5 minutes. Differential BAL cell counts were made from total counts of 400 cells using a leukostat stain kit (Fisher Scientific, Orangeburg, NY) and nonspecific esterase stain (Sigma Diagnostic, St. Louis, MO) for better definition of mononuclear phagocytes. Bronchoalveolar lavage cells were enriched for lymphocytes by the nylon wool column technique. Alveolar macrophages and polymorphonuclear lymphocytes were removed by this technique. Almost all eluted cells were stained negative for nonspecific esterase and possessed lymphocyte morphology. Natural killer cells were not removed by this purification step [10]. Bronchoalveolar lavage lymphocytes were then adjusted to appropriate concentration (5×10^6 cells/mL) for cytotoxic assays. All BAL fluid samples were sent for standard bacterial cultures. Three different samples were positive for moderate growth of gram-negative bacilli, and those 3 animals were excluded from the study. The data presented here came from the group of 8 remaining animals free of bacterial contamination.

PERIPHERAL BLOOD LYMPHOCYTES. Heparinized venous blood samples were obtained together with BAL. Peripheral blood lymphocytes were isolated by Ficoll-Paque discontinuous-gradient density technique. Cells were washed three times with RPMI-complete medium and adjusted to appropriate concentration for cytotoxic assays.

Cytotoxic Assays

NATURAL KILLER CELL ASSAY. Canine thyroid adenocarcinoma cells served as target for NK cells [11]. One hundred microliters of effector cells (either BAL lymphocytes or peripheral blood lymphocytes) were added to 10^4 ^{51}Cr-labeled target cells in round-bottom, 96-well tissue culture plates at effector to target ratios of 50:1, 25:1, and 12.5:1. Assays were done in triplicate. After incubation at 37°C in 5% CO_2-humidified air for 6 hours, the culture plates were centrifuged at 0°C for 5 minutes at 1,000 rpm. From each well, 100 μL of supernatant was harvested and radioactivity was assessed in a gamma scintillation counter. Percentage cytotoxicity (% specific target lysis) was calculated by a standard formula, using the mean values of triplicate cultures: % cytotoxicity = (CPM experimental − CPM spontaneous release)/(CPM total release − CPM spontaneous release) × 100, where CPM = counts per minute.

Spontaneous release was determined in wells containing target cells and medium alone. Total release was determined by incubating target cells with 100 μL of 0.5% Triton X100 detergent. Spontaneous release was always less than 5% of total release.

LECTIN-DEPENDENT CELL-MEDIATED CYTOTOXICITY ASSAY. This assay is regarded as a quantitative measurement of the total cell-mediated cytotoxicity of a T cell population [12–14]. Raji cells (derived from human Burkitt's lymphoma) were used as targets. It was performed like the NK cell assay with the addition of the lectin concanavalin A to the assay medium at the concentration of 8 μg/mL.

HANDLING OF TARGET CELLS. Target cells were maintained in culture in RPMI-complete medium and split 1 to 5 every 4 days. Three days before assay, a portion of the cells was brought to a concentration of 2×10^5/mL to ensure that the target cells were actively dividing on the day of cytotoxic assays. Labeling of target cells was performed as follows: 2×10^6 cells were suspended in 300 μL of RPMI-complete medium and 200 μL of Tris-phosphate buffer solution (pH = 7.4). One hundred μCi of sodium chromate ^{51}Cr (I.C.N. Canada; specific activity, 250 Ci/mg Cr) were added to cell suspensions. They were incubated at 37°C in 5% CO_2 humidified air for 1 hour with frequent shaking every 15 minutes. Cells were washed twice with the culture medium and then adjusted to 10^5/mL. For assays, 100 μL (10^4 cells) was added to each well.

Table 1. Total and Differential Counts of Bronchoalveolar Lavage Cells From Normal Lungs and Atelectatic Right and Unaffected Left Lower Lobes

Lung Area	Total (10^4/mL)	M (10^4/mL) (%)	Lymph (10^4/mL) (%)	PML (10^4/mL) (%)
Normal	14.6 ± 2.0	10.7 ± 1.1 (75.8 ± 4.8)	2.4 ± 0.4 (17.7 ± 3.3)	1.5 ± 0.2 (8.5 ± 2.8)
RLL	65.4 ± 17.2	18.2 ± 4.0 (28.1 ± 5.4)	10.1 ± 2.0 (15.5 ± 2.5)	37.1 ± 8.0 (57.2 ± 11.0)
LLL	19.0 ± 2.3	14.0 ± 2.0 (74.0 ± 5.0)	2.8 ± 0.3 (15.0 ± 4.0)	2.2 ± 0.4 (11.2 ± 2.4)

Values are shown as mean ± standard deviation.

LLL = unaffected left lower lobe; Lymph = lymphocyte; M = macrophage; PML = polymorphonuclear leukocytes; RLL = atelectatic right lower lobe.

Statistical Analysis

Results were all presented as mean ± standard deviation. For clarity, all postoperative lung and blood NK and LDCMC activities were shown as percentage of preoperative levels. Data were compared using the paired *t* test and *p* values less than 0.05 were considered significant.

Results

The endobronchial balloon catheter technique employed in this study succeeded in producing lobar atelectasis in all subjects (with no associated complications). Atelectasis was confirmed radiographically in each animal. There was a mild febrile reaction and peripheral blood leukocytosis in all atelectatic animals.

Cell yields from BAL before induction of atelectasis and of unaffected left lower lobes were 14.6 ± 2.0 × 10^4 and 19.0 ± 2.3 × 10^4 cells/mL, respectively (p = not significant). Cytological examination of these two lavage cell populations revealed a similar differential count of 75% macrophages, 17% lymphocytes, and 8% polymorphonuclear leukocytes, which is comparable with previous findings by Whitelaw and others [15, 16]. Lavages of atelectatic right lower lobes yielded a significantly higher number of cells (65.4 ± 17.2 × 10^4 cells/mL; $p < 0.001$), which was composed mainly of polymorphonuclear leukocytes (57%) and correspondingly lower percentages of alveolar macrophages and lymphocytes. However, there was a significant increase in the absolute number of lymphocytes harvested from atelectatic lung segments (10.1 ± 2.0 × 10^4 lymphocytes/mL versus 2.4 ± 0.4 × 10^4 lymphocytes/mL in normal lung; $p < 0.01$) (Table 1).

The effects of atelectasis on NK and LDCMC activity of lung and blood lymphocytes are shown in Figures 1 and 2 (cytolytic activities at 50 to 1 of effector to target cell ratio were expressed as percentages of preoperative controls). Atelectasis was associated with a significant reduction of NK and LDCMC activity in BAL lymphocytes. Although NK activity remained unchanged in the left unaffected lungs, it was decreased to about 60% of normal level in the right atelectatic lung segments. Similarly, LDCMC activity was also reduced to about 65% of the preoperative level after atelectasis. The difference was significant ($p < 0.01$ by paired *t* test between the means of percentage changes of atelectatic right lower lobe and contralateral normal left lower lobe). On the other hand, NK and LDCMC activity in peripheral blood lymphocytes was drastically increased, up to 160% of the preoperative level, in atelectatic animals ($p < 0.01$) (see Fig 2).

Comment

Pulmonary atelectasis may occur separately after trauma and operation or it may constitute an important component of many other acute and chronic lung diseases. In addition to demonstrating the likelihood of specific derangements in the local immune cell phenotype and function in the atelectatic lung, we have recently been interested in the use of BAL as a method of differentiating various types of lung pathology such as lung allograft rejection from pneumonia or atelectasis. This study, in particular, attempts to further elucidate the mechanisms

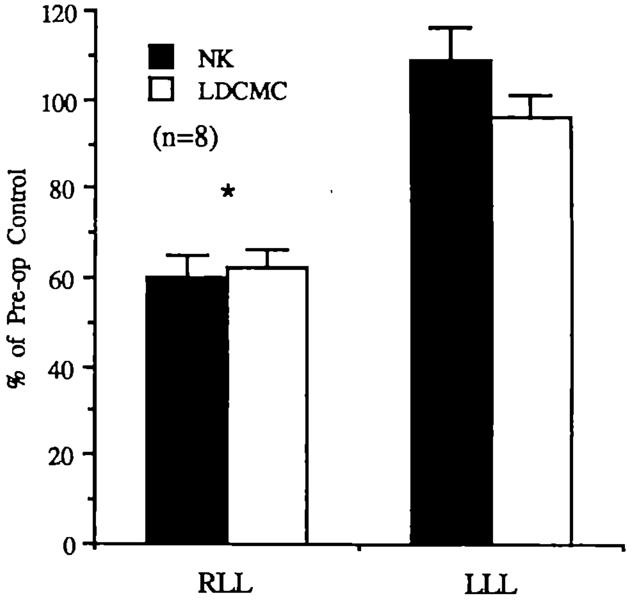

*Fig 1. Natural killer (solid bars) and lectin-dependent cell-mediated cytotoxicity (open bars) in normal left lower lobe (LLL) and atelectatic right lower lobe (RLL) at 50:1 effector to target ratio. Although cytotoxicity of lung lymphocytes remained unchanged in normal LLL, atelectasis was associated with a significant decrease in natural killer (NK) and lectin-dependent cell-mediated cytotoxicity (LDCMC) activity (*p < 0.01). Changes were expressed as percentage of preoperative control values.*

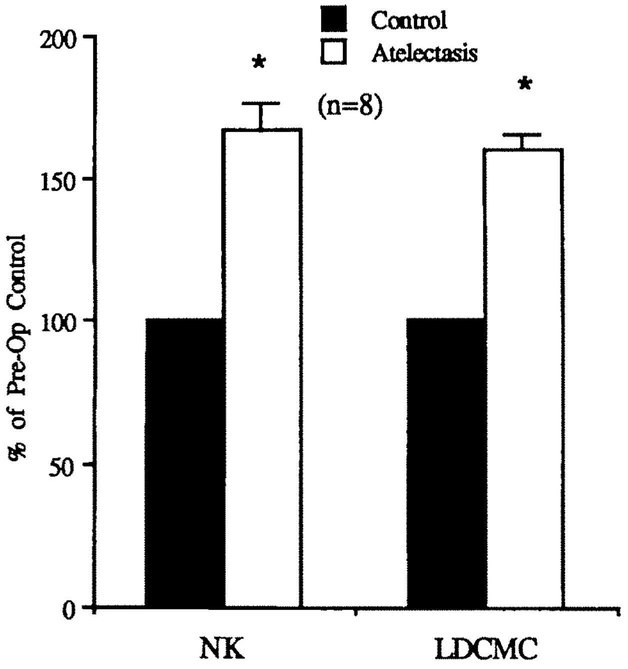

Fig 2. The effect of atelectasis on peripheral blood natural killer (NK) and lectin-dependent cell-mediated cytotoxicity (LDCMC). There was a significant increase in NK and LDCMC activity in peripheral blood lymphocytes of animals having atelectasis of the right lower lobes (open bar, *$p < 0.01$). *changes were expressed as percentage of preoperative control values.*

of pulmonary sepsis that frequently follow the development of atelectasis.

Previously, we have shown that atelectasis impairs lung host defenses by decreasing the ability of alveolar macrophages to phagocytose bacteria. Alveolar macrophages are the primary cellular line of defense in the lower respiratory tract [17, 18]; however, they are not the only immunocompetent cells in the alveolar space. Recruited lymphocytes have been identified in the normal respiratory tract of different species including humans in variable proportions [19–21]. Morphologic and functional characterizations of alveolar lymphocytes in a canine model and in human subjects indicate the presence of both thymus dependent (T) and bone-marrow-derived (B) lymphocytes [16, 22]. They seem to originate from or transit through the bronchus-associated lymphoid tissue [23, 24]. Lymphocytes are recruited to the alveolar spaces and are activated by airborne antigens to provide local specific immunity [25, 26]. Activated lymphocytes in turn interact with local pulmonary alveolar macrophages via lymphokines to augment the latter's phagocytic and bactericidal activity [27].

We observed an increase in the absolute lymphocyte and polymorphonuclear leukocyte counts in the BAL cells harvested from the atelectatic lung. The recruitment of lymphocytes and polymorphonuclear leukocytes to the collapsed lung segments suggests a local production of chemotactic substances within the atelectatic lungs. Alveolar macrophages have been previously shown to be capable of releasing such chemotactants [28]. It also substantiated previous findings of Daniele and associates [22], who observed an accumulation of lymphocytes and polymorphonuclear leukocytes within the airspace in response to local inflammation of the lung.

The LDCMC assay was adapted by Emerson and colleagues [12] to the canine model to study cytotoxic T lymphocytes using a xenogeneic target. It is generally regarded as a measurement of the total cytotoxicity of a T cell population [13, 14]. The canine NK cell is featured as a large granular lymphocyte [11], similar to NK cells of other species [29]. One of its in vitro characteristics is spontaneous cytotoxicity against a variety of tumor cells. Its in vivo function is thought to involve, among others, immunosurveillance against virus-infected host cells and neoplasms, and hematopoietic and B cell regulation [30–32]. Recently, canine NK cells have been studied by Loughran and co-workers [11] using a cytotoxic assay and the canine thyroid adenocarcinoma cell line as target cell. In this study, we assessed the lung and blood lymphocyte immune function by using the in vitro quantitative NK and cytotoxic T lymphocyte assays. We observed an impairment of cell-mediated immunity in the atelectatic lung segments. It occurred uniformly in all effector to target cell ratios of the in vitro NK and LMCMC assays (data not shown). This observation is complementary to our previous findings of alveolar macrophage dysfunction after atelectasis [3]. The mechanism by which T lymphocyte function becomes impaired is not clear. Variables within the collapsed lung that may contribute to such impairment of T lymphocyte function include an inhibitory effect by alveolar macrophages [33] or recently recruited polymorphonuclear leukocytes to alveolar space, a decrease in local oxygen tension, and the release of inhibitory mediator(s) in the atelectatic lung [34, 35]. The monocyte/macrophage lineage has been shown to play an important down-regulatory role on NK cell cytolytic function [36]. The impaired NK cell function observed in this study may conceivably be mediated by local alveolar macrophages in the presence of atelectasis. Cytotoxicity of lymphocytes from unaffected left lower lobes that were exposed to the same experimental conditions (except atelectasis) as those from the affected right lower lobes were unchanged from preoperative control values (see Fig 1), indicating that changes of lymphocyte cytotoxicity in the right lower lobes are in fact due to atelectasis.

It has also been interesting to observe a discrepancy between the local lung and systemic peripheral blood immune responses to this kind of pulmonary pathology. The importance of the augmentation of systemic cell-mediated cytotoxicity seen 2 days after the induction of atelectasis while local lung immunocompetent cells showed functional impairment remains unclear. One would expect that inflammatory mediators such as interleukin 1 or tumor necrosis factor released to systemic circulation from the injury site would affect both local and systemic immune cell populations in a similar manner. It is possible that, as indicated by our findings, atelectasis induces an unfavorable local microenvironment for optimal lung cellular host defenses. This compartmentalization of the immune response, however, has been observed in other forms of lung injuries [37]. The mechanisms underlying such a systemic activation of circulating cytotoxic lymphocytes after lobar atelectasis deserve further investigation.

We conclude from this study that atelectasis is associated with a significant impairment of its local bronchoalveolar lymphocyte cytotoxic function. Considering the role played by these cells in the local lung host defenses, one can presume that such an impairment in NK and T cell cytotoxic function may render atelectatic lungs more susceptible to infection.

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Amiodarone Versus Bretylium for Suppression of Reperfusion Arrhythmias in Dogs

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Reperfusion arrhythmias are an important complication of interventions to limit infarct size. Recently, amiodarone has been shown to be rapidly effective in suppressing sustained, incessant ventricular tachycardia and ventricular fibrillation in this setting. This study evaluated the time course of arrhythmia suppression and comparative efficacy of amiodarone versus bretylium in a canine model of reperfusion arrhythmias. Of 23 dogs subjected to a Harris two-stage coronary artery ligation followed by release, 18 demonstrated clinically significant ventricular arrhythmias and received either intravenous amiodarone, 5 mg/kg (9 dogs), or intravenous bretylium, 5 mg/kg (9 dogs). Direct-current shocks for sustained ventricular tachycardia or ventricular fibrillation were administered as necessary. Amiodarone rapidly suppressed sustained ventricular tachycardia and ventricular fibrillation in this model with no dog in the amiodarone-treated group requiring cardioversion after completion of the 15-minute infusion versus 4 of 9 dogs in the bretylium-treated group ($p < 0.05$). Amiodarone was more effective than bretylium in suppressing episodes of sustained ventricular tachycardia/ventricular fibrillation, episodes of nonsustained ventricular tachycardia, and premature ventricular complexes. The blood pressure and heart rate decreased more after amiodarone administration than after bretylium administration. We conclude that, in the canine reperfusion arrhythmia model, amiodarone is rapidly effective in suppressing ventricular arrhythmias and is more effective than bretylium.

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With the advent of a variety of acute interventions to prevent infarction or limit infarct size by restoring myocardial blood flow after a period of ischemia, reperfusion arrhythmias have become increasingly important. Recently, intravenous amiodarone has been demonstrated to be rapidly effective in suppressing sustained, incessant ventricular tachycardia (VT) or ventricular fibrillation (VF) in acute postoperative settings where reperfusion may have been the responsible mechanism [1]. Furthermore, in emergency settings, some investigators have found intravenous amiodarone effective even after bretylium had failed [1–5]. In those studies, amiodarone appeared to be rapidly effective and to be superior to bretylium. If this were the case, it may be advantageous to use amiodarone before bretylium or other antiarrhythmic agents, because the likelihood of a successful outcome is adversely affected by a prolonged resuscitative effort. However, those studies did not allow exclusion of the possibility that the drug combination or the additional elapsed time required to administer a second drug was responsible for the observations rather than amiodarone's rapid efficacy. Thus, the purpose of this study was to determine the time course of amiodarone's antiarrhythmic efficacy in a canine reperfusion model and to perform a direct comparison of amiodarone versus bretylium in this setting.

Material and Methods

A group of 23 adult mongrel dogs, weighing 15 to 30 kg, were studied. General anesthesia was induced and maintained with sodium pentobarbital. Endotracheal intubation was performed and the animals were ventilated with room air using a mechanical ventilator. After a median sternotomy and vertical pericardiotomy, cannulas were placed into the right femoral vein, the right femoral artery, and the left and right atrial appendages. The surface electrocardiogram and arterial, left atrial, and right atrial pressures were recorded continuously on a Grass Model 5 Polygraph (Grass Instrument Co, Quincy, MA). A two-channel Holter Monitor (Oxford Instruments, Oxford, England) was attached via needle electrodes. Arrhythmia records were stored on cassette tapes and hand counted at a later time. Normothermia was maintained with a heating pad and heating lamps. Arterial blood for partial pressures of oxygen and carbon dioxide, pH, and oxygen saturation, and venous blood for sodium, potassium, and calcium determinations were obtained before initiating the protocol after 15 minutes of ventilator support, during coronary ligation, and at the completion of the experiment. Adequate intravascular volume was maintained with lactated Ringer's solution. All experiments conformed to the Guiding Principles in the Care and Use of Laboratory Animals as approved by the Case Western Reserve University Animal Resource Facility.

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Harris Two-Stage Coronary Ligation

A Harris two-stage coronary ligation was performed followed by release after 30 minutes of complete occlusion [6]. The proximal left anterior descending coronary artery was isolated between the first and second diagonal branches and controlled with a vascular sling. The first stage of ligation consisted of partial occlusion with a 1-0 silk tie incorporating an 18-gauge blunt needle, which was removed as soon as the tie was made. This partial stenosis was maintained for 30 minutes. The second stage of ligation was complete occlusion with an atraumatic vascular clamp. This was also maintained for 30 minutes. The clamp and tie were rapidly removed after the second stage.

Arrhythmia Treatment Protocol

Complex ventricular arrhythmias were defined as VF, sustained VT, nonsustained VT, or frequent (>5/min) premature ventricular complexes. During clamping and for the first 5 minutes of reperfusion, episodes of VF or sustained VT were treated with direct-current countershocks without concomitant drug therapy. After 5 minutes of reperfusion, dogs with one or more forms of complex ventricular arrhythmias received amiodarone or bretylium in an alternate fashion. Both drugs were administered as infusions of 5 mg/kg over 15 minutes through a femoral venous catheter. If arrhythmias persisted or recurred within 15 to 30 minutes of infusion of the first dose, a second dose of 10 mg/kg was administered. If no arrhythmias were observed after 120 minutes, the animal was excluded from analysis.

Electrical countershocks were administered as necessary for sustained VT or VF during the 4-hour observation period. Shocks were delivered via an internal active spoon electrode and an external back ground plate. Initial shocks of 20 J were used. If the arrhythmia did not terminate after two attempts at this setting, the energy was increased to 50 and then to 100 J.

Analysis of Data

All data were analyzed using an IBM System 2 Model 60 Personal Computer and Number Cruncher Statistical System Version 5.01 software package (NCSS 865 E. 400 North, Kaysville, UT). Log transformations were used when data were not normally distributed (nonsustained VT and premature ventricular complex data). Data were first analyzed using analysis of variance and covariance with repeated measures looking for differences over time and between groups. If analysis of variance showed significant differences between groups, unpaired t tests were performed to examine group differences during specific time intervals. Categorical data (the combined data for VT and/or VF) were analyzed using the Fisher's exact test. The null hypothesis was rejected at $p < 0.05$.

Results

The protocol was attempted in 23 dogs. In 18 experiments complex ventricular arrhythmias were observed after the 5-minute postreperfusion waiting period; these dogs received amiodarone (9 dogs) or bretylium (9 dogs). In the amiodarone group, 5 dogs had sustained VT or VF before therapy, and in the bretylium group, 4 dogs had sustained VT or VF before therapy. In 5 experiments complex ventricular arrhythmias were not observed after 5 minutes of reperfusion and no drug was administered.

Arrhythmia Suppression

The hourly frequencies of episodes of sustained VT and/or VF are shown in Figure 1A for the 18 treated dogs. Over the 4-hour treatment period, there were two episodes of sustained VT or VF in the amiodarone-treated group and nine episodes in the bretylium-treated group ($p < 0.03$ by Fisher's exact test). After 15 minutes of therapy (the time of completion of the drug infusions), no dog in the amiodarone-treated group versus 4 of 9 dogs in the bretylium-treated group demonstrated one or more of these malignant arrhythmias ($p < 0.05$ by Fisher's exact test).

Episodes of nonsustained VT were observed significantly less often in the amiodarone-treated group (Fig 1B). This difference was significant during hours 1, 2, and 4 of the experiment ($p < 0.05$).

Over the 4-hour study period episodes of premature ventricular complexes were reduced significantly more by amiodarone (33.58 episodes/hour) than by bretylium (92.53 episodes/hour) (Fig 1C) ($p < 0.03$).

During the 4-hour study period, 1 dog in the amiodarone-treated group required a second bolus of 10 mg/kg for frequent premature ventricular complexes and 7 dogs in the bretylium-treated group required a second bolus of 10 mg/kg for complex ventricular arrhythmias (4 for premature ventricular complexes and 3 for VF) ($p < 0.05$ by Fisher's exact test).

Heart Rate and Hemodynamic Response

Relative to baseline values, blood pressure decreased after amiodarone therapy, from a mean of 113 ± 19 mm Hg before therapy to a nadir of 62 ± 8 mm Hg at 30 minutes of therapy ($p < 0.0001$) (Fig 2 top, squares). In the bretylium-treated group the blood pressure was 110 ± 15 mm Hg before therapy and 100 ± 21 mm Hg after 4 hours ($p = 0.16$) (Fig 2 top, circles). During the first 90 minutes of therapy the blood pressure reduction observed with amiodarone therapy was significantly greater than that observed with bretylium ($p < 0.0001$).

The heart rate decreased after the administration of amiodarone from 167 ± 14 to 122 ± 11 beats/min after 30 minutes of amiodarone therapy ($p < 0.0001$) (Fig 2 bottom, squares). The rate then slowly increased over the next 4 hours to 157 ± 15 beats/min. In the bretylium-treated group there was no significant change in heart rate over the 4-hour treatment period ($p = 0.82$) (Fig 2 bottom, circles). There was no statistical difference in heart rate response between the amiodarone-treated group and the bretylium-treated group ($p = 0.69$).

The differences in left and right atrial pressures were not significant between drugs or over time. There were no differences over time or between groups when comparing hydrogen ion concentration, partial pressures of carbon dioxide and oxygen, and levels of sodium, potassium, calcium, bicarbonate, and hemoglobin.

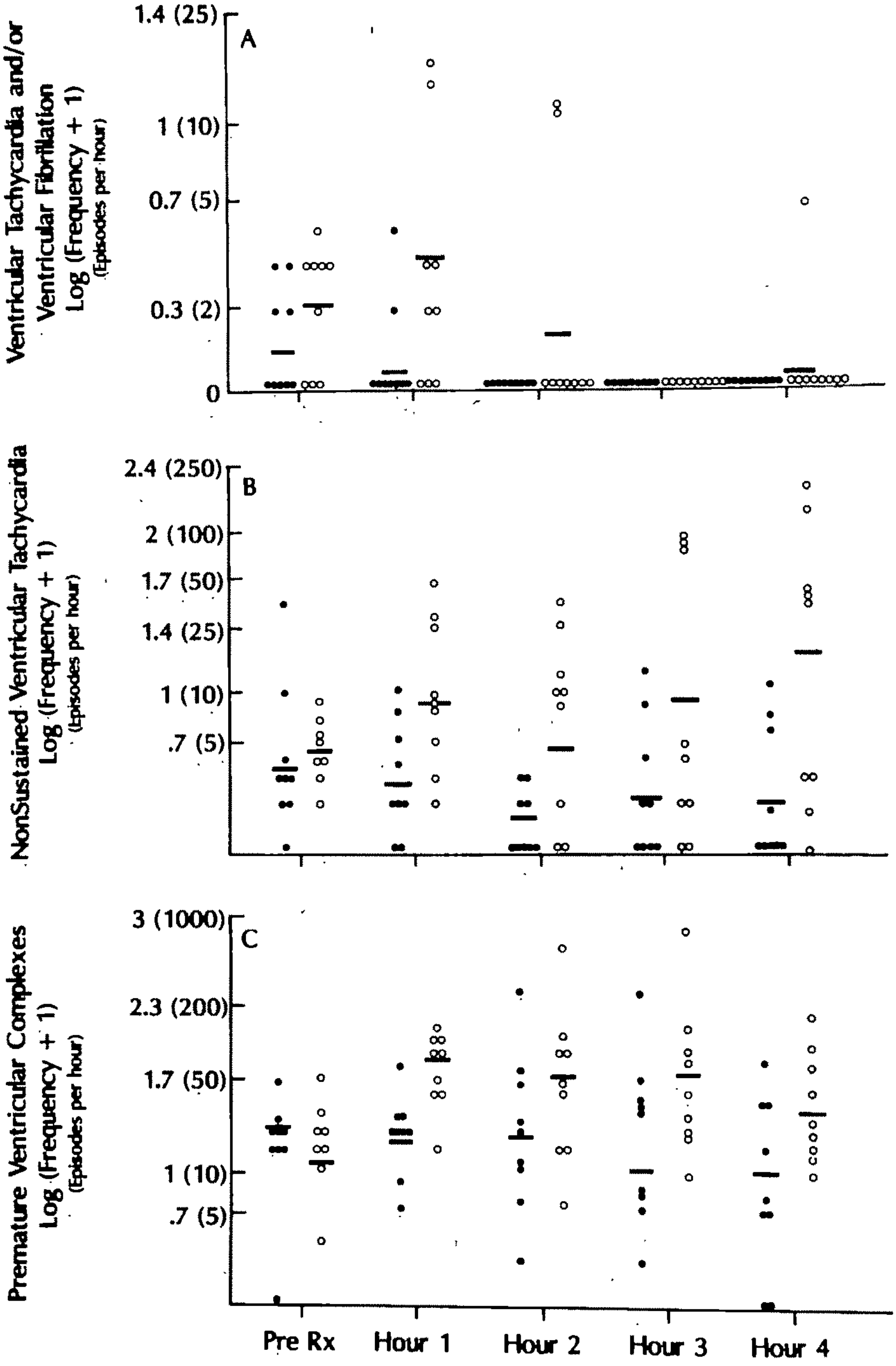

Fig 1. Episodes of sustained ventricular tachycardia or ventricular fibrillation (A), nonsustained ventricular tachycardia (B) and premature ventricular complexes (C) before and during drug therapy with amiodarone (closed circles) *and bretylium* (open circles). *Arrhythmias were recorded on continuous tape. Counts were grouped hourly and displayed as the log of the frequency plus 1. The numbers in parentheses represent the actual counts observed. The* bars *represent the means of the log data used in statistical analysis.*

Comment

This study evaluated the efficacy of amiodarone in treating reperfusion arrhythmias in anesthetized dogs. Both the time course of arrhythmia suppression and the efficacy relative to bretylium were examined. In this setting, amiodarone was rapidly effective in suppressing the most malignant arrhythmias, with no dog in the amiodarone group requiring cardioversion or defibrillation after the 15-minute dose of drug had been administered. Amiodarone was also more effective than bretylium in this model. In the group of dogs treated with amiodarone, there were fewer episodes of sustained VT or VF, nonsustained VT, and premature ventricular complexes. Thus, in this canine reperfusion arrhythmia model, amiodarone was superior to bretylium in efficacy and had an onset of action of 15 minutes or less.

Mechanisms of Drug Action

The superiority of amiodarone over bretylium in this model may be explained by the multiple mechanisms of action that the drug possesses. Although both amiodarone and bretylium have Vaughn-Williams class III activity, intra-

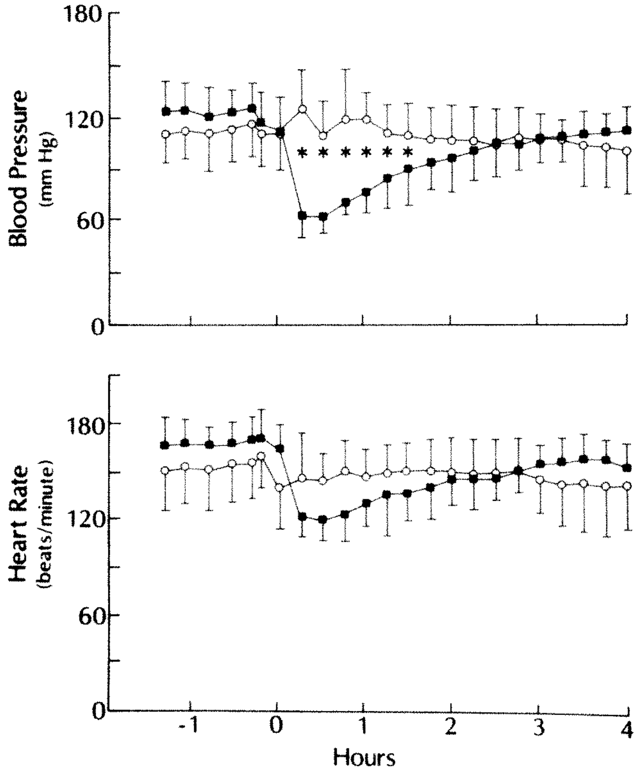

Fig 2. Blood pressure (top) and heart rate (bottom) response to amiodarone (squares) *and bretylium* (circles). *Blood pressure and heart rate were measured at 15-minute intervals before and for 4 hours after drug infusion. The infusion began at hour 0. Data are means with standard deviation bars. (* $p < 0.05$ *between drug groups.)*

venous amiodarone exerts several other short-term effects. Several investigators have demonstrated immediate effects on fast (sodium) channel activity after the administration of intravenous amiodarone [7–10]. Amiodarone blocks slow (calcium) channel conductance [11, 12]. The acute β-blocking properties of amiodarone may be playing a role [13–16]. Amiodarone possesses antiischemic effects in part mediated by coronary and peripheral vasodilating properties [14, 17, 18]. α-Blocking properties have been shown to be antiarrhythmic in experimental models of reperfusion arrhythmias due to early afterdepolarizations caused by cesium [19, 20]. Because intravenous amiodarone possesses α-blocking properties, it may be exerting an antiarrhythmic effect via this mechanism [21]. Also, the blood pressure response was different in the two groups. Thus, the differences in arrhythmias may have been caused by mechanisms related to sympathetic tone or coronary perfusion.

Mechanism of Arrhythmia

A striking finding in this study is the rapid onset of action of amiodarone. This contrasts with the several-day delay in onset of action often observed when amiodarone is used to treat chronic recurrent VT. A possible explanation for the rapid effect observed in the present study is that the mechanism responsible for the arrhythmias in the chronic versus the acute setting may be different. In our institution the majority of patients who have received intravenous amiodarone for cardiac emergencies have been immediately after coronary artery bypass grafting and have had an acute ischemic insult with probable reperfusion. To simulate the clinical situation where intravenous amiodarone was rapidly effective we chose a canine model of ischemic injury followed by reperfusion, and, as in the clinical setting, arrhythmia suppression was observed rapidly. This represents a different arrhythmia substrate from the patients with chronic recurrent VT, whose arrhythmias are usually based on a reentry mechanism. Thus the time required for onset of action may be dependent on the mechanism of the arrhythmia in addition to the mechanism of action of the drug.

Rationale for Study Design

The goal of this study was to compare equipotent doses of amiodarone and bretylium in a setting that closely resembled our clinical experiences, during which we noted amiodarone to be more effective than bretylium. The Harris two-stage coronary ligation model was used to minimize arrhythmias during coronary ligation [6]. The 30-minute total occlusion period was selected to maximize reperfusion arrhythmias [22, 23]. This model has been shown to produce ischemic injury [24]. Identical drug administration methods (5 mg/kg over 15 minutes) were selected to compare the two agents. More rapid injection of amiodarone produces substantial hypotension and a decrease in cardiac output in patients with reduced left ventricular function [25]. Bretylium, 5 mg/kg, has been used both as a bolus and as an infusion administered over 15 minutes [26]. Although some patients responded to bretylium within minutes, others responded only after delays of several hours. Anderson and associates [27] studied the time course of the antifibrillatory action of bretylium in a canine model of temporary ischemia. After a bolus of 6 mg/kg, antifibrillatory effects were apparent within 2 minutes. However, bretylium's electrophysiologic effects correlated with myocardial concentrations. The myocardial concentrations required 1.5 to 6 hours to achieve a plateau after a bolus injection. Thus, whether bretylium is administered as a bolus or as a 15-minute infusion, an antiarrhythmic effect may be seen within minutes but maximal antiarrhythmic efficacy may be seen only after a substantial delay. The lack of a significant increase and then decrease in blood pressure and heart rate after bretylium administration was not consistent with observations in humans [26]. However, using an anesthetized canine model, Wenger and co-workers [28] also noted no change in these variables over 70 minutes after a 10-minute infusion of bretylium, 10 mg/kg.

In our study, there were large individual differences in responses over time, which resulted in the observation of no net change. Thus, the finding of no net change may reflect the complexity of bretylium's adrenergic effects rather than a lack of drug effect.

Limitations of Study

A limitation of this study is the absence of a placebo control group. However, bretylium has been shown to be effective in suppressing reperfusion arrhythmias. Thus, demonstrating amiodarone's superiority to bretylium in this setting also demonstrates its superiority to placebo.

Another limitation is the absence of drug maintenance infusions after the initial dose. Latini and colleagues [29] have shown in dogs that the serum concentration of amiodarone decreases quite rapidly after a single bolus of amiodarone, 5 mg/kg, but that myocardial concentrations peak after 5 to 30 minutes and remain near the peak concentration for 2 hours. Anderson and associates [27] have reported similar findings with bretylium, with myocardial concentrations achieving a peak at approximately 1 hour and remaining near this level for 12 hours. In that study antifibrillatory effects of bretylium correlated better with myocardial concentrations than with serum concentrations. In both of these studies, serum and myocardial concentrations were detectable for several hours after the single dose of drug. The method and dose of drug administered in the present study was nearly identical to that used in the studies by Anderson and associates [27] and Latini and colleagues [29]. Thus, it is unlikely that the absence of a maintenance infusion resulted in drug inefficacy during this 4-hour study.

Conclusions

We conclude that amiodarone is rapidly effective in the suppression of reperfusion-induced ventricular arrhythmias in dogs. It is also superior to bretylium in this setting. Because clinical outcome may be adversely affected by the length of the resuscitation, these data justify the direct comparison of amiodarone and bretylium in humans with refractory incessant VT or VF requiring cardiopulmonary resuscitation and multiple direct-current countershocks in situations where the mechanism responsible for the arrhythmias may be reperfusion.

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Traumatic Asphyxia

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During a 5-year period, we treated 14 cases of traumatic asphyxia. There were 12 male and 2 female patients ranging in age from 2 to 32 years. Most suffered crushing injuries at work or were run over by motor vehicles. Mild to severe cervicofacial cyanosis and petechiae developed in all patients. A fear response was reported by 12 of the patients. Subconjunctival hemorrhage was also found in 12 patients. Nine patients had tachypnea and 7 complained of dyspnea. Most of the patients suffered some associated injuries including 8 head injuries, 7 pulmonary contusions, and 6 cases of blunt abdominal trauma. Less-associated injuries were rib fractures, brachial and radial nerve injuries, hemothorax, and pneumothorax. The hospital stay ranged from 4 to 28 days (mean, 14 days) and follow-up from 10 to 60 months (mean, 32 months). Treatment for traumatic asphyxia included measurement of arterial blood gases, oxygen supplementation, and intubation with mechanical ventilation. The patients' recovery conditions were relative to the severity of injury and the associated injuries.

(Ann Thorac Surg 1991;51:86–8)

The classic syndrome of traumatic asphyxia includes cervicofacial cyanosis, subconjunctival hemorrhage, ecchymosis, and petechiae of the face, usually secondary to blunt trauma (Fig 1). These were first observed by Ollivier [1] in 1837; he termed the syndrome "masque ecchymotique" when noting these characteristic features in a patient trampled to death by crowds in Paris. It was not until 1900 that Perthes [2] made a more extensive review and detailed its pathophysiology and features including mental dullness, hyperpyrexia, hemoptysis, tachypnea, and contusion pneumonia. Since then, there have been a number of series discussing its pathophysiology and mechanisms of injury, but all hypotheses remain controversial.

In 1968, Williams and associates [3] suggested the fear response was an important factor in the production of craniofacial petechiae. The fear response is defined as the feeling of impeding doom as the patient realizes he or she is about to be crushed.

This is a 4-year review of our experience with and results of cases of traumatic asphyxia.

Material and Methods

We retrospectively collected 14 cases of patients who sustained thoracoabdominal compressive injury with clinical features of cervicofacial cyanosis or facial petechiae (Table 1). They were all admitted through our emergency room to our cardiovascular intensive care unit from May 1984 until December 1988. Patients sustaining severe associated injuries who died on arrival in our emergency department were excluded. There were 12 male and 2 female patients. The ages ranged from 2 to 32 years.

Patients were stabilized in the emergency department, including intubation if required, before elucidation of the history. Arterial blood gas measurements, chest roentgenography, and any other indicated studies were then performed.

Among our 14 patients, 9 suffered from thoracic, abdominal, or thoracoabdominal crushing injuries at work, 3 were run down by motor vehicles, 1 was compressed by a steering wheel, and the final 1 had a crushing force on the right side of the chest.

On questioning 12 of our patients reported a fear response just before the crushing. Clinical features of cervicofacial cyanosis and petechiae of the head and neck regions developed in all patients in varying degrees (severe, 4; moderate, 7; mild, 3). Subconjunctival hemorrhage developed in 12 patients. Other commonly noted symptoms were disturbance of consciousness (3), tachypnea (9), and dyspnea (7).

Two patients were in shock; 1 of them had left diaphragm rupture and the other had multiple long bone fractures. All other patients were hemodynamically stable.

Other associated injuries included head injuries in 8 patients, with variable changes in the Glasgow Coma Scale. None had surgical lesions. Six patients had abdominal tenderness with elevation of serum glutamic-oxaloacetic transaminase level. Only the patient with the left diaphragmatic rupture with herniation of the stomach and intestine required operation.

Results

The initial arterial blood gas results revealed the lowest oxygen tension levels in the 7 patients who were found to

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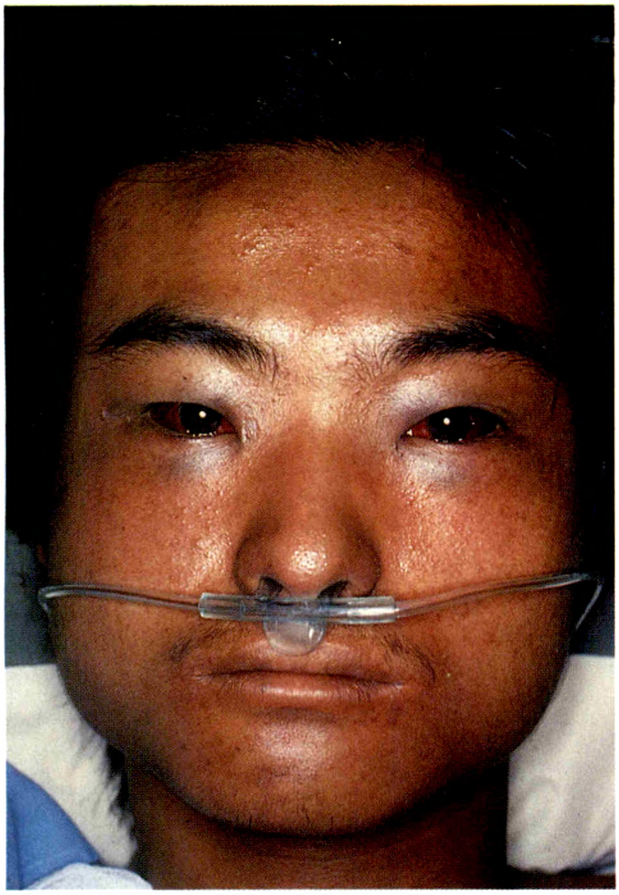

Fig 1. Prominent features of traumatic asphyxia include cervicofacial cyanosis with multiple petechiae and subconjunctival hemorrhage.

have pulmonary contusions on chest roentgenogram. Four of these patients were intubated for pulmonary care or head injury protection. All other patients were treated with oxygen supplementation alone, and all patients seemed to recover well. The hospital stay varied from 4 to 28 days with a mean of 14 days. The follow-up period ranged from 10 to 60 months with a mean of 32 months.

Most patients recovered with no sequelae. The only morbidity was due to associated injuries: 1 patient had subglottic stenosis with a tracheocutaneous fistula after prolonged intubation, and another patient had a radial nerve injury with an incomplete recovery.

Comment

In 1866, Tardieu [4] offered the first explanation that "the punctiform ecchymosis of the face, neck and chest are caused by the effort in which resistance to suffocation manifested itself." Heuter [5] later had two hypotheses: first, a mechanical reflux of blood out of the compressed chest into the valveless veins of the head and neck leading to venular and capillary atony and stasis cyanosis, and second, that contusion of the abdominal sympathetic nerves causes vasodilation of the head and neck region. Bolt [6], in his study, postulated four factors: (1) deep inspiration, (2) closure of glottis, (3) thoracoabdominal effort, eg, splinting of thoracic and abdominal musculature, and (4) thoracic or abdominal compression that forces blood into the cervicofacial regions producing venular and capillary stasis.

More recently, Reichert and Martin [7] in 1951 in canine experiments found that occlusion of the superior vena cava alone could cause a considerable congestion of the upper extremities and head regions, but they were not able to duplicate the clinical features of traumatic asphyxia. In 1968, Williams and associates [3] concluded that just at the moment of impending disaster, a fear response is practically always present. This fear reflex would lead the patient to take a deep breath, hold it, and brace himself or herself. The closed epiglottis would then enhance greatly the intrathoracic pressure during compression.

In 1989, Thompson and co-workers [8] found that valves can only play a limited role in the protection of venous beds against high pressure, but the elevated intraabdominal pressure developed during the fear response followed by an acute abdominal thoracic compression can cause collapse of the inferior vena cava, thereby protecting the lower torso from the venous injury seen in traumatic asphyxia.

The striking physical characteristics include multiple punctiform petechiae and bluish discoloration extending over the face, neck, and sometimes the upper part of the chest to the level of nipples anteriorly and approximately to the lower level of trapezius posteriorly. The petechiae practically never reach the elbow laterally. These petechiae usually blanch on pressure and almost always increase in intensity over the first few hours and then gradually fade over days to weeks. Frequently, they are associated with mild to massive subconjunctival hemorrhage, periorbital edema, and ecchymosis. Immediate impairment or loss of vision has also been reported as a result of retinal edema, but may promptly recover within hours or days. Permanent vision loss is very rare.

Neurologically, the syndrome initially manifests primarily as agitation, restlessness, and disorientation. Williams and associates [3] suggested these neurological signs may be associated with minor intracranial hemorrhage or cerebral edema. These are usually reversible within 24 hours without any sequelae.

In our series, associated injuries were frequently encountered especially involving the brain, thorax, and abdomen. With major pulmonary complications such as severe pulmonary contusion or flail chest, therapy mainly involved respiratory support. In cases of minor chest injury, administration of oxygen therapy by nasal cannula or mask was sufficient.

Our experience indicates that patient prognosis depends on the morbidity of associated injuries. The victim may die within minutes due to severe associated injuries, or may need long-term rehabilitation if neurological damage or long bone fractures have been sustained. For those patients with pure traumatic asphyxia syndrome who survive to the emergency room, a full recovery should be expected.

Table 1. Cases of Traumatic Asphyxia

Patient No.	Age (y)	Sex	Mechanism	Signs and Symptoms	Associated Injuries	Hospital Stay (d)	Complications
1	32	M	Thoracoabdominal compression	Moderate ME[a]	BAT	5	. . .
2	24	M	Steering-wheel compression	Moderate ME	Multiple ribs fracture, lung contusion, facial laceration	10	. . .
3	10	M	Abdominal compression	Mild ME	BAT	4	. . .
4	24	F	Chest compression	Moderate ME	Left brachial plexus injury	25	. . .
5	26	M	Chest compression	Moderate ME	Lung contusion with R pneumothorax, R scapular fracture	18	. . .
6	32	M	Thoracoabdominal compression	Severe ME	Flail chest BAT, brain edema	13	. . .
7	4	M	Chest compression	Severe ME, shock	Head injury, L diaphragm hernia	27	Subglottic stenosis
8	27	M	Chest compression	Moderate ME	Back 3° burn, brain edema	19	. . .
9	16	M	Abdominal compression	Moderate ME	Rib fracture, pulmonary contusion, brain edema	11	. . .
10	2	M	Thoracoabdominal compression	Mild ME	Pulmonary contusion, BAT, rib fracture, head injury	11	. . .
11	18	M	Crush with roller machine	Severe ME, shock	BAT, R humerus fracture, both femoral fracture	23	R radial nerve palsy
12	4	F	Run down by bus	Mild ME	Trunk abrasion wound	(AAD)	. . .
13	28	M	Run down by bus	Severe ME	Head injury, trunk abrasion	28	. . .
14	22	M	Run down by truck	Moderate ME	Head injury, pulmonary contusion	12	. . .

[a] Moderate ME: as in Figure 1; mild ME: petechiae only localized on periorbital and cervical region; severe ME: petechiae become confluent over whole cervicofacial region.

AAD = against advice discharge; BAT = blunt abdominal trauma; ME = masque ecchymotique; 3° = third-degree.

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Role of Potassium Concentration in Cardioplegic Solutions in Mediating Endothelial Damage

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We studied the effect of potassium concentration in cardioplegic solutions on endothelial function by examining its influence on 5-hydroxytryptamine- (5-HT) and nitroglycerin-induced vasodilation in the isolated rat heart. Forty-eight rat hearts were perfused on a modified Langendorff preparation. After a baseline record of increase in coronary flow induced by 10^{-7} M 5-HT and 10 μg/mL nitroglycerin, the hearts were perfused for 30 or 60 minutes with either St. Thomas' solution or Bretschneider solution containing 20 mmol/L of potassium or for 30 minutes with either solution containing 30 mmol/L of potassium (n = 8 in each). Initially, 5-HT and nitroglycerin caused a 39.0% ± 3.3% and 39.7% ± 2.8% increase in coronary flow, respectively. After 30 or 60 minutes' perfusion with St. Thomas' solution containing 20 mmol/L of potassium, there was little change in the response to 5-HT or nitroglycerin (5-HT, 43.1% ± 4.1%; nitroglycerin, 38% ± 3.2%). Similarly, perfusion with Bretschneider solution (20 mmol/L K^+) for 30 or 60 minutes did not alter the degree of vasodilation (5-HT, 39.2% ± 2.9%; nitroglycerin, 38.0% ± 3.3%). However, perfusion with St. Thomas' solution containing 30 mmol/L of potassium for 30 minutes abolished the endothelial-dependent 5-HT-induced vasodilation (5-HT, −1.6% ± 1.4%; nitroglycerin, 36.9% ± 2.2%). Perfusion with Bretschneider solution (30 mmol/L K^+) gave similar results (5-HT, −2.1% ± 1.2%; nitroglycerin, 36.4% ± 1.7%). We conclude that the concentration of potassium in cardioplegic solutions plays a critical role in causing functional endothelial damage.

(Ann Thorac Surg 1991;51:89–93)

Crystalloid cardioplegic solutions have been in widespread clinical use for operative myocardial protection. Though the principles of cardioplegia-induced myocardial protection are well established [1, 2], the optimum concentration of various agents and the nature of additives have not been standardized, thereby leading to a variety of crystalloid cardioplegic solutions in clinical use with varying concentrations of principle ingredients and with different additives. Currently the most commonly used cardioplegic agent is potassium in the concentration of 15 to 35 mEq/L [3].

Potassium is a known vascular irritant and has been used to denude the vessels of endothelium [4]. The cytotoxicity of hyperkalemic crystalloid cardioplegic solutions to cultured endothelial cells has been demonstrated by Carpentier and associates [5] and Solberg and coworkers [6]. However, the effect of potassium concentration in cardioplegic solutions on endothelial function has not been studied.

We [7] have previously shown that 5-hydroxytryptamine (5-HT) causes a dose-dependent increase in coronary flow in the isolated perfused rat heart that is dependent on an intact endothelium and that this model could be used to study the effect of various agents thought to have a deleterious effect on coronary vascular endothelium. In this study, we have used this model (isolated perfused rat heart) to investigate the effect of potassium concentration in two different cardioplegic solutions in causing functional damage to the coronary vascular endothelium

Material and Methods

Animals and Reagents

Hearts were obtained from male AO/Olac rats (body weight, 300 to 350 g) that had been maintained on a standard laboratory diet. 5-hydroxytryptamine was obtained from Sigma Chemicals Ltd, St. Louis, MO; Nitroglycerin, from Dupont (UK) Ltd; and St. Thomas' Hospital cardioplegic solution from Macarthy Medical, Romford, Essex, UK. Bretschneider solution was prepared by the Pharmacy at Harefield Hospital. All the animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Perfusion Technique

Rats were anesthetized with halothane. The chest was opened and 200 units of heparin was injected into the right ventricle. After about 60 seconds, the heart was excised and immersed in a beaker containing Krebs-Henseleit bicarbonate buffer [8] with the following composition (mmol/L): NaCl, 118.07; KCl, 4.69; $MgSO_4 \, 7H_2O$, 1.18; KH_2PO_4, 1.18; $NaHCO_3$, 25.0; glucose, 11.1; and $CaCl_2$, 2.5. The heart was then mounted onto a modified Langendorff preparation [9] that allowed accurate measurement of coronary flow at a constant perfusion pressure (100 cm H_2O) from any one of four reservoirs.

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Table 1. Composition of St. Thomas' Hospital Cardioplegic Solution[a]

Component	Potassium 20 mmol/L	Potassium 30 mmol/L
Sodium chloride (mmol/L)	147.0	147.0
Potassium chloride (mmol/L)	20.0	30.0
Magnesium chloride (mmol/L)	15.7	15.7
Calcium chloride (mmol/L)	2.0	2.0
Procaine hydrochloride (mmol/L)	1.0	1.0

[a] pH = 5.5 to 7.5; osmolality = 300 to 320 mosm/L.

Table 2. Composition of Bretschneider Cardioplegic Solution[a]

Component	Potassium 20 mmol/L	Potassium 30 mmol/L
Sodium chloride (mmol/L)	12.0	12.0
Potassium chloride (mmol/L)	20.0	30.0
Magnesium chloride (mmol/L)	2.0	2.0
Procaine hydrochloride (mmol/L)	7.3	7.3
Mannitol (mmol/L)	238.7	238.7

[a] pH = 6.0 to 7.5; osmolality = 320 to 340 mosm/L.

Hearts were perfused through the aorta with ultrafiltered (5-μm filter) Krebs-Henseleit buffer and gassed with 95% O_2 plus 5% CO_2 (pH 7.4 at 37°C.). Drugs used in the experiments were dissolved in the buffer at the desired concentration and were gassed uniformly throughout the study.

After the first 10-minute stabilization period, during which the coronary flow was measured continuously, the hearts were perfused with 10^{-7} mmol/L 5-HT for 3 minutes. Coronary flow was recorded for the last 2 minutes of perfusion with 5-HT. The coronary circulation was washed with the drug-free buffer for the next 12 minutes to reestablish the basal coronary flow. The hearts subsequently were perfused with nitroglycerin (10 μg/mL) for 3 minutes and the coronary flow was measured for the last 2 minutes of perfusion. The mean increase in coronary flow after 5-HT and nitroglycerin perfusion was calculated and expressed as a percentage over the control value.

After the establishment of baseline response of the coronary vasculature to 5-HT and nitroglycerin, the hearts were perfused continuously at 20°C for 30 or 60 minutes with either St. Thomas' hospital solution or Bretschneider solution containing 20 mmol/L of potassium or for 30 minutes with either solution containing 30 mmol/L of potassium. The composition of these solutions is shown in Tables 1 and 2. Coronary flow was measured for the total duration.

The hearts were then rewarmed by perfusing with Krebs-Henseleit buffer at 37°C for 15 minutes during which the basal coronary flow was reestablished. Perfusion with 10^{-7} mmol/L 5-HT and 10 μg/mL of nitroglycerin was repeated for 3 minutes with a 12-minute wash-out period in between and the percentage change in coronary flow calculated as before.

Pilot experiments were performed to find the optimum perfusion time with drug-free buffer required to achieve stabilization, to establish the perfusion time required for 5-HT and nitroglycerin to produce the maximal response, and to standardize the period of wash-out with the drug-free buffer required to reestablish the basal coronary flow after drug-induced changes in coronary flow.

In additional studies, it was demonstrated that the hearts perfused with the buffer for a period of 2 hours maintained a similar response to 5-HT and nitroglycerin.

Expression of Results

Coronary flow was measured continuously. Values used for determining the changes in coronary flow were taken during the last 4 minutes before changing to perfusion with the drug-containing buffer and during the last 2 minutes of perfusion with 5-HT and nitroglycerin. Changes in coronary flow were expressed as a percentage of the control value. Eight hearts were used in each experimental protocol. All data were expressed as the mean ± standard error of the mean. Statistical analysis was performed by unpaired Student's *t* test.

Table 3. Percentage Increase in Coronary Flow Induced by 5-Hydroxytryptamine (10^{-7} mmol/L) and Nitroglycerin (10 μg/mL) Before and After Continuous Infusion of St. Thomas' and Bretschneider Cardioplegic Solutions Containing 20 mmol/L of Potassium for 30 Minutes in the Isolated Rat Heart

	% Increase in Coronary Flow			
	5-Hydroxytryptamine		Nitroglycerin	
Solution	Before	After	Before	After
St. Thomas'	37.9 ± 4.4	45.1 ± 3.9[b]	45.2 ± 3.9	44.0 ± 3.6[b]
Bretschneider	37.8 ± 3.1	39.4 ± 3.7[b]	36.8 ± 2.5	36.6 ± 2.6[b]

[a] n = 8. [b] *p* = not significant.

Table 4. Percentage Increase in Coronary Flow Induced by 5-Hydroxytryptamine (10^{-7} mmol/L) and Nitroglycerin (10 μg/mL) Before and After Continuous Infusion of St. Thomas' and Bretschneider Cardioplegic Solutions Containing 20 mmol/L of Potassium for 60 Minutes in the Isolated Rat Heart[a]

	% Increase in Coronary Flow			
	5-Hydroxytryptamine		Nitroglycerin	
Solution	Before	After	Before	After
St. Thomas'	42.9 ± 4.0	41.2 ± 4.3[b]	38.6 ± 4.2	32.0 ± 2.8[b]
Bretschneider	44.1 ± 3.9	39.0 ± 2.2[b]	40.9 ± 3.5	39.4 ± 4.0[b]

[a] n = 8. [b] p = not significant.

Results

Both 5-HT and nitroglycerin initially caused an increase in the coronary flow. After continuous infusion of the two solutions containing 20 mmol/L of potassium for 30 minutes, there was no significant difference in the percentage increase in the coronary flow induced by 5-HT or nitroglycerin (Table 3). Continuous infusion of St. Thomas' or Bretschneider solution containing 20 mmol/L of potassium for 60 minutes maintained the basal vasodilatory response of coronary vasculature to 5-HT and nitroglycerin (Table 4). In contrast, continuous infusion for 30 minutes of St. Thomas' solution containing 30 mmol/L of potassium completely abolished the 5-HT–induced increase in coronary flow (36.8% ± 2.3% increase in flow before versus 1.6% ± 1.4% decrease in flow after the infusion, $p < 0.001$); however, nitroglycerin-induced vasodilation was not affected (38.1% ± 2.9% increase in flow before and 36.9% ± 2.2% increase after the infusion, p = not significant) (Fig 1A). Continuous infusion of Bretschneider solution containing 30 mmol/L of potassium had a similar effect on the response to 5-HT and nitroglycerin (Fig 1B). 5-Hydroxytryptamine and nitroglycerin caused a 34.6% ± 2.2% and 38.4% ± 1.9% basal increase in the flow, respectively. After the infusion, 5-HT caused a mild vasoconstriction (2.1% ± 1.2% decrease in the flow, $p < 0.001$) but the vasodilaton induced by nitroglycerin was well maintained (36.4% ± 1.7% increase in the flow, p = not significant).

Comment

In the present series of experiments, we have demonstrated that continuous infusion for 60 minutes of cardioplegic solutions containing 20 mmol/L of potassium is not detrimental to endothelial function. Our experimental protocol is only slightly at variance with the clinical practice, where after a single dose of cardioplegia, the heart is arrested and a second dose is administered after a variable period of time. During the period of cardioplegic arrest, the potassium is slowly washed out of the coronary circulation by noncoronary collateral flow [10]. In this study, we have used the continuous infusion technique to avoid ischemic endothelial damage. Both the duration of the continuous infusion and the temperature of the solution were selected to approximate the clinical situation.

Under these experimental conditions, we have shown that an increase of the potassium concentration from 20 mmol/L to 30 mmol/L without any alteration in the components or dosage of St. Thomas' or Bretschneider solution is highly detrimental to endothelial function. The conversion of a 5-HT–induced vasodilatory response to a slight vasoconstriction after high-potassium cardioplegia infusion was not due to any alteration in the vascular

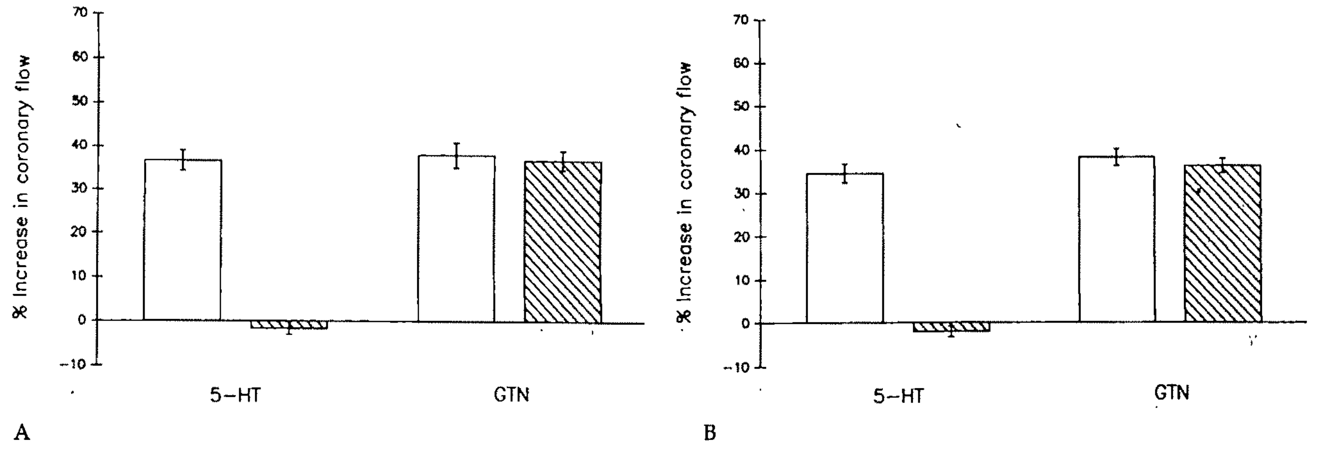

Fig 1. Percentage increase in coronary flow induced by 5-hydroxytryptamine (5-HT) (10^{-7} mmol/L) and nitroglycerin (GTN) *(10 μg/mL) before* (open bars) *and after* (hatched bars) *the continuous infusion of St. Thomas' solution (A) or Bretschneider solution (B) containing 30 mmol/L of potassium for 30 minutes in the isolated rat heart (n = 8 in each). (The negative value indicates reduction in the flow.)*

smooth muscle responsiveness as nitroglycerin-induced vasodilation remained unchanged. We [7] have previously shown that in the isolated rat heart, 5-HT causes coronary vasodilation by releasing endothelium-derived relaxing factor and that when the release of endothelium-derived relaxing factor is blocked or when the endothelium is damaged, the vasoconstrictive effect of 5-HT on the coronary vasculature is unmasked. Therefore, the apparent reduction in coronary flow after high-potassium cardioplegia is a reflection of endothelial damage. Our findings are in agreement with those of Saldanha and Hearse [11].

Solberg and co-workers [6] studied the effect of cardioplegic solutions on cultured human endothelial cells. They concluded that the presence of procaine increased the injurious effect of the solutions. The two solutions used in this study differed widely with regard to their procaine concentration. However, our results indicate that in the isolated rat heart, high concentration of procaine per se is unlikely to cause endothelial dysfunction.

Potassium is a known vascular irritant [12] and has been shown to cause endothelial damage of vein grafts in animal models [13, 14]. Hoover and co-workers [13] exposed the canine jugular vein at low pressure to hyperkalemic lactated Ringer's solution (K^+, 40 mEq/L) for several minutes and then grafted into the external carotid artery. At 6 weeks, the grafts exposed to hyperkalemic solution showed intense adventitial fibrotic reaction under light microscopy suggesting a full-thickness graft injury as compared with the normal-looking controls. In the primate model of vein graft atherogenesis, Olinger and associates [14] have shown significantly higher cholesterol accumulation in cephalic vein grafts exposed to hyperkalemic solution (27 mEq/L) when evaluated at 3 months after implantation. This phenomenon is most likely to be related to endothelial injury.

Endothelial damage could have important clinical implications. Intact endothelium produces prostacyclin, antithrombin III, plasminogen activator, heparan sulfate, and α_2-macroglobulin [15–19]. This prevents platelet aggregation and fibrin deposition on the vessel wall. Platelet deposition on the damaged endothelium in the early postoperative period could lead to reperfusion injury [20, 21]. Endothelial damage could also result in early graft occlusion or the long-term complication of graft atherosclerosis [22]. Because the action of a majority of vasoactive endogenous and exogenous agonists is strongly modulated by the basal and stimulated release of endothelium-derived relaxing factor, endothelial damage can have a profound effect on tissue perfusion by unmasking the receptor-mediated direct vasoconstrictive effect [23, 24] of these agents. This could have an adverse effect on myocardial function especially in the early postoperative period or could produce irreversible myocardial damage.

Other investigators have provided evidence that hyperkalemic cardioplegic solutions damage coronary vascular endothelium [5, 25–27]. Carpentier and associates [5] evaluated the cytotoxicity of 12 different cardioplegic solutions using tissue culture technique. They found that the percentage of dead endothelial cells after 3 hours' incubation in various cardioplegic solutions at 19°C ranged from 4.7% to 13.1% (4.5% dead cells in the control solution). Solberg and co-workers [6] studied the effects on cultured human endothelial cells of incubation with St. Thomas' and Bretschneider cardioplegic solutions at 10° or 20°C by measuring release of chromium 51 from the prelabeled cells and by electron microscopy. They demonstrated that there was mild to moderate injury to the cells after 1 or 5 hours of incubation with either solution. Using morphological means, Harjula and associates [26] also demonstrated coronary endothelial damage after use of crystalloid cardioplegia. These studies provide evidence of the cytotoxic effect of potassium on the endothelium but differ from the clinical situation as either cultured cells were incubated with cardioplegic solutions [5, 6, 27] or ischemia time was prolonged without repeating the cardioplegia [26], thereby increasing the possibility of ischemia-induced endothelial damage.

In summary, we have shown the critical role of potassium concentration in cardioplegic solutions in causing functional endothelial damage. Therefore, the potassium concentration in cardioplegic solutions should be optimized not only to protect the myocardium but also to prevent endothelial damage.

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Might Free Arterial Grafts Fail Due to Spasm?

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The rat femoral artery was used as a free graft and was studied after 2, 7, 14, 30, and 60 days. The patency of the grafts was 100% (2 days, n = 6), 78% (7 days, n = 9), 63% (14 days, n = 8), 33% (30 days, n = 12), and 18% (60 days, n = 11). Histology showed an intimal thickening after 14 days and the media, which in the controls consisted of eight to ten layers of myocytes, was reduced to six to eight cell layers. During the first 2 weeks the graft segments had an impaired contraction when exposed to Krebs solution with 124 mmol/L K^+, whereas after 1 month and later the graft segments approached the controls or had even higher contractile force. The thromboxane mimic U-46619 elicited full contractile force at all times whereas the potency was significantly lower during the first 14 days. Noradrenaline was unable to induce contraction in the graft segments during the first 14 days, but at 30 and 60 days it had regained full contractile force and was significantly more potent (approximately 60 times) in the graft segments compared with the controls. This study suggests that intimal thickening and hypercontractility might be a problem in free muscular arterial grafts.

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Arm veins used as aortocoronary bypass grafts have a high failure rate compared with saphenous vein grafts [1]. The internal mammary artery used as an in situ graft has a much higher late patency rate than a comparable saphenous vein graft [2, 3]. Inspired by these facts several surgeons have started to use free arterial grafts in the revascularization of the ischemic heart [4–11] hoping that they will be as good as the in situ mammary artery graft or at least better than the saphenous vein graft. However, some factors might play a potentially negative role when comparing a free versus an in situ arterial graft.

The free graft is totally denervated, and this might influence the number or the function of the important postjunctional contraction-mediating α-adrenergic receptors. Another factor is that the circulation of blood and lymph in the vasa vasorum is totally disrupted in the free graft, which might cause medial necrosis and intimal thickening [12–14]. Will such a changed intima retain its full capacity to produce relaxing or antithrombotic factors [15, 16]?

In a postoperative angiographic study an "unexpected finding" was that three of ten free right gastroepiploic artery grafts had major vasospasm [17]. In other studies most of the free radial artery aortocoronary bypass grafts failed within 1 year [5, 13]. Might spasm be a problem with free arterial grafts? Spasm is known to occur in mammary and gastroepiploic arteries used as in situ grafts [18–23], but this is not at present generally recognized to be of clinical significance. The present study was designed with the aim of elucidating some contractile properties of a free arterial graft.

Material and Methods

Operation

Forty-four male Sprague-Dawley rats weighing 300 g were anesthetized with 75 mg chloral hydrate intraperitoneally. The left femoral artery was exposed and gently dissected free from the iliofemoral vein. The superficial circumflex iliac artery was ligated and cut and a 10- to 12-mm segment of the femoral artery could thus be extirpated between two arterial clamps placed at the inguinal ligament and at the deep femoral artery. The free arterial graft was kept in chilled (4°C) Ringer's solution for 30 minutes and then reimplanted into the femoral artery keeping the original orientation. A Zeiss OPMI 6-S operating microscope was used. Eight interrupted stitches of 10-0 polyglycolic acid (Vicryl; Ethicon) were used at each anastomosis.

The rats were randomized into five groups. After 2, 7, 14, 30, and 60 days the rats were again anesthetized and the femoral artery was dissected free and cut just distal to the distal anastomosis. If blood ejected from the proximal cut end the graft was deemed patent. If no blood was coming out of the graft, the graft was dissected out and cut into five ring segments, which were investigated under the operative microscope to be sure that the lumen really was occluded.

The patent graft was cut into five ring segments (each about 2 mm in length) and immediately brought into tissue baths. A 2-mm ring segment was also taken from the right femoral artery and used as a control. All surgical procedures were done by the same surgeon. The study was approved by the Ethics Committee of the University of Lund. The animals were treated in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

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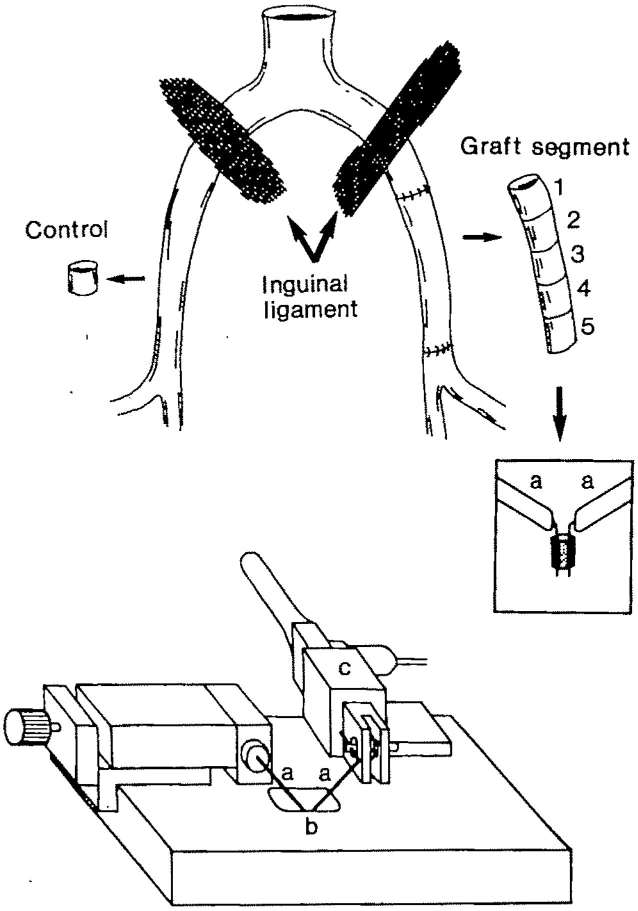

Fig 1. The graft implanted in the left femoral artery was excised and divided into five segments. These and a control segment obtained from the contralateral side were mounted between two L-shaped metal holders (a) in organ baths (b). One of the metal holders is connected to a force displacement transducer (c).

Recording of Mechanical Activity

The ring segments were suspended between two L-shaped metal holders (0.17 mm in diameter) arranged in parallel. One of the metal holders was attached to a Grass FT 03 C force-displacement transducer (Fig 1). The output from the transducer was amplified by and displayed on a Grass polygraph. The other holder was fixed to a movable unit. By a micrometer screw the movable unit could be displaced and a resting tension applied to the vessel. The vessel segments were submerged in temperature controlled (37°C) tissue baths containing 5 mL Krebs solution (for composition, see "Buffer Solutions" section). The baths were bubbled with oxygen containing 5% carbon dioxide, giving a pH of approximately 7.4. The vessels were repeatedly stretched until a basal tension of about 6 mN was reached. In separate experiments in healthy 2-mm ring segments from rat femoral arteries it was ascertained that a maximal contractile response was obtained at this basal tension. They were allowed to equilibrate in the baths for 1 to 2 hours before the experiments started. Six vessel segments could be investigated simultaneously.

Experimental Procedure

Repeated contractions were induced by a preheated (37°C) and bubbled (95% O_2 + 5% CO_2) K^+-rich Krebs solution (for composition, see "Buffer Solutions" section) until the amplitude of two subsequent contractions varied less than 10%. The maximum response was used as an internal standard to which subsequent agonist-induced contractions were related. First noradrenaline and then, after repeated washes resulting in a return to the basal tension, the thromboxane analogue U-46619 were added cumulatively to all vessel segments.

Buffer Solutions

The Krebs buffer solution contained (in mmol/L): NaCl, 119; $NaHCO_3$, 15; KCl, 4.6; NaH_2PO_4, 1.2; $MgCl_2$, 1.2; $CaCl_2$, 1.5; and glucose, 11. The K^+-rich solution was prepared by substituting all NaCl in the Krebs solution with equimolar amounts of KCl.

Drugs

Dilutions of (-)-noradrenaline hydrochloride (Sigma) were made in NaCl containing 1 mmol/L ascorbic acid. U-46619 (9,11-dideoxy-11α,9α-epoxymethano-prostaglandin $F_{2\alpha}$; Upjohn) was prepared to a stock solution in absolute ethanol (5 mg/mL) and stored at −20°C. Fresh dilutions of U-46619 were made with phosphate buffer at neutral pH just before use. The concentrations are given as final molar concentrations in the tissue baths.

Analysis of Data

The maximum contraction (E_{max}) produced by each agonist was determined. The contraction was regarded as maximum when two subsequent contractions gave responses of the same amplitude or when the subsequent concentration produced a decreased contraction amplitude. The pEC_{50} value, ie, the negative logarithm of the EC_{50} value, was determined graphically from each curve as the concentration giving half-maximal contraction. The pEC_{50} value was not calculated if the maximum contraction obtained with an agonist was less than 10% of the K^+-induced contraction. Wilcoxon's test for unpaired data was used for statistical comparisons.

Histology

After the organ bath experiments the specimens were fixed in 4% phosphate-buffered (pH = 7.0) formalin-saline solution. Then they were sectioned and stained with hematoxylin-eosin and van Gieson's stain for elastin.

Results

Patency of the Grafts

All grafts were patent after 2 days; thereafter the patency decreased to 18% after 60 days (Table 1).

Histological Examination

After 2 and 7 days the intima was not changed as deemed from light microscopic studies with ×400 magnification (Fig 2A–C). After 14, 30, and 60 days an intimal thickening

Table 1. Patency of the Free Arterial Grafts

Days	No. of Grafts	No. of Patent Grafts	Patency (%)
2	6	6	100
7	9	7	78
14	8	5	63
30	12	4	33
60	11	2	18

could be seen (Fig 2D–F). The media, which in the controls consisted of eight to ten cell layers of myocytes, was reduced to six to eight cell layers (Fig 2E–F), whereas the adventitia had increased in thickness (Fig 2B–F).

The nonpatent grafts at 7 and 14 days were occluded by thrombotic material. The nonpatent grafts in the 30-day and 60-day groups were like fibrous strings and no distinct cell layers could be identified.

Responses to Potassium-Rich (124 mmol/L) Krebs Solution

Two days after the grafting procedure the contractile response to potassium in the graft segments was only about one third of the control. Segment 4, which had the highest mean value (2.53 ± 0.85 mN), was significantly lower ($p < 0.05$) than the control (6.65 ± 0.97 mN). On days 7 and 14 the response to potassium in the graft segments had increased to about 50% compared with their controls. However, no significant difference was found between the segment producing the highest contractile response and the control. After 30 days the graft segments approached the control and after 60 days some graft segments elicited even higher contractile force (Fig 3). During the first 2 weeks the segments adjacent to the

Table 2. Drug Effect on Patent Graft Segments and Controls

		Noradrenaline			U-46619		
Day	Segment	E_{max}	pEC_{50}	z	E_{max}	pEC_{50}	z
2 (n = 6)	1	0	. . .	0	66 ± 6	6.1; 7.0	2
	2	0	. . .	0	107 ± 16	6.5 ± 0.2	6
	3	0	. . .	0	95 ± 15	6.2 ± 0.1	6
	4	0	. . .	0	92 ± 25	6.4 ± 0.3	5
	5	0	. . .	0	51 ± 16	6.5 ± 0.3	4
	Control	98 ± 6	4.6 ± 0.5	6	106 ± 3	8.5 ± 0.6	5
7 (n = 7)	1	0	. . .	0	56 ± 6	6.6 ± 0.1	7
	2	6 ± 4	8.5	1	89 ± 13	6.9 ± 0.1	7
	3	10 ± 4	7.4 ± 0.6	3	86 ± 14	7.7 ± 0.5	7
	4	20 ± 11	6.5 ± 0.1	3	86 ± 12	7.4 ± 0.3	7
	5	3 ± 3	7.0	1	80 ± 8	6.8 ± 0.1	7
	Control	96 ± 17	4.9 ± 0.4	7	137 ± 21	8.4 ± 0.2	7
14 (n = 5)	1	0	. . .	0	0	. . .	. . .
	2	0	. . .	0	72 ± 27	7.2 ± 0.1	3
	3	0	. . .	0	121 ± 12	7.7 ± 0.1	4
	4	11 ± 11	5.5	1	125 ± 17	7.5 ± 0.2	4
	5	9 ± 6	6.8; 6.1	2	110 ± 26	7.4 ± 0.3	4
	Control	102 ± 10	6.0 ± 0.6	5	146 ± 10	9.3 ± 0.3	5
30 (n = 4)	1	24 ± 14	6.5; 6.4	2	100 ± 47	8.2 ± 0.7	3
	2	89 ± 30	6.7 ± 0.4	3	182 ± 65	8.9 ± 0.6	3
	3	103 ± 8	5.6 ± 1.0	4	146 ± 35	8.2 ± 0.3	4
	4	103 ± 13	5.8 ± 0.8	4	142 ± 28	8.4 ± 0.8	4
	5	47 ± 23	6.6; 6.7	2	96 ± 20	7.7 ± 0.7	4
	Control	124 ± 2	4.8 ± 0.6	3	148 ± 20	9.1 ± 0.7	4
60 (n = 2)	1	0; 52	7.3	1	0; 135	8.3	1
	2	108; 92	6.6; 6.6	2	142; 124	7.8; 8.0	2
	3	118; 58	6.1; 7.3	2	218; 138	7.7; 7.7	2
	4	147; 102	6.7; 5.8	2	200; 148	7.7; 7.9	2
	5	150; 96	6.5; 6.2	2	180; 119	7.6; 7.8	2
	Control	150; 101	4.8; 5.5	2	217; 108	7.8; 7.7	2

E_{max} = contraction in percent of the maximum K^+ (124 mmol/L)-induced contraction; n = number of rats with patent grafts; pEC_{50} = negative logarithm of concentration giving 50% of E_{max}; z = number on which pEC_{50} is based (see Material and Methods).

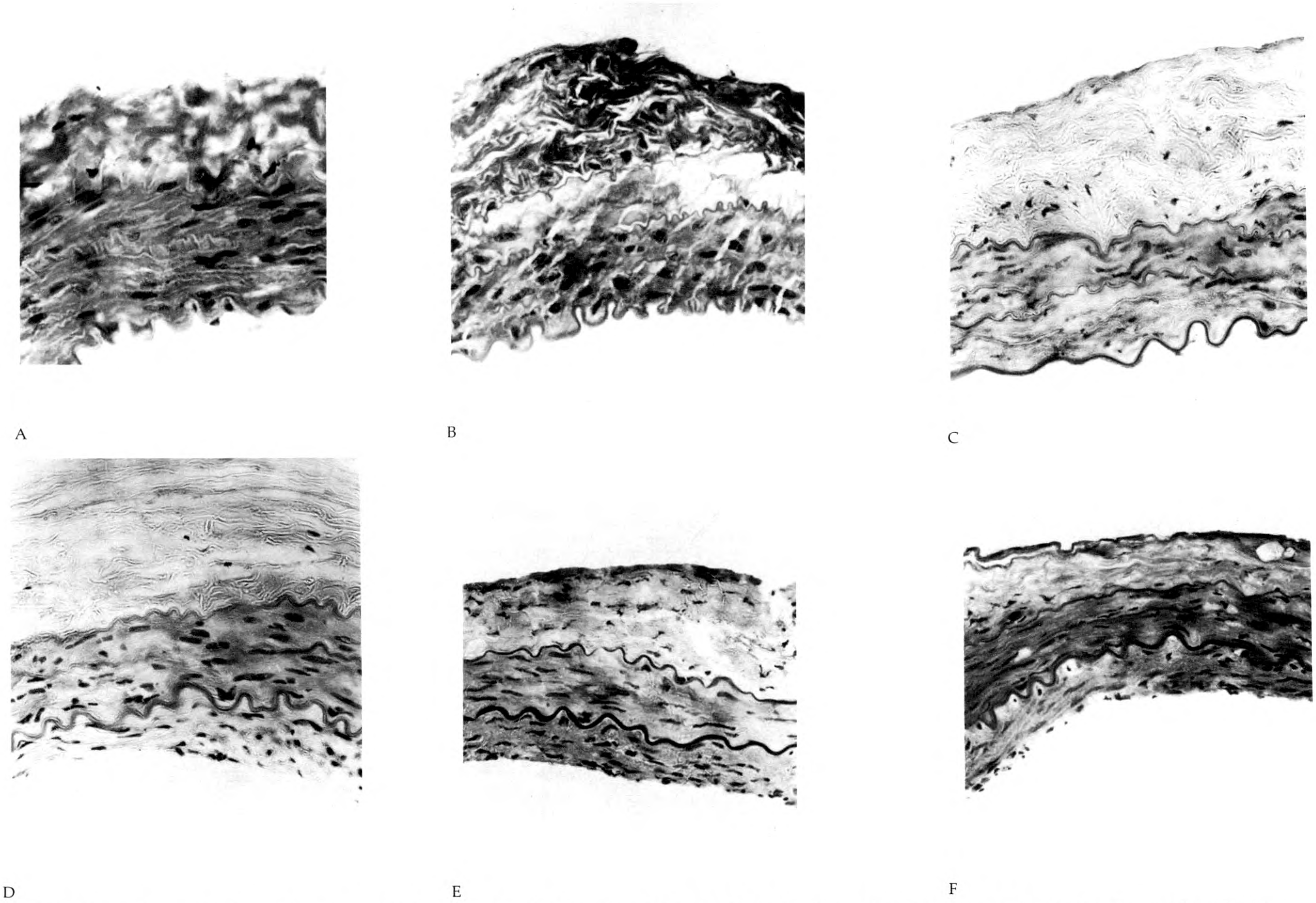

Fig 2. *Histology of the free arterial grafts: (A) control, (B) 2 days, (C) 7 days, (D) 14 days, (E) 30 days, and (F) 60 days. Intimal thickening can be seen from day 14. (Hematoxylin and eosin, ×400).*

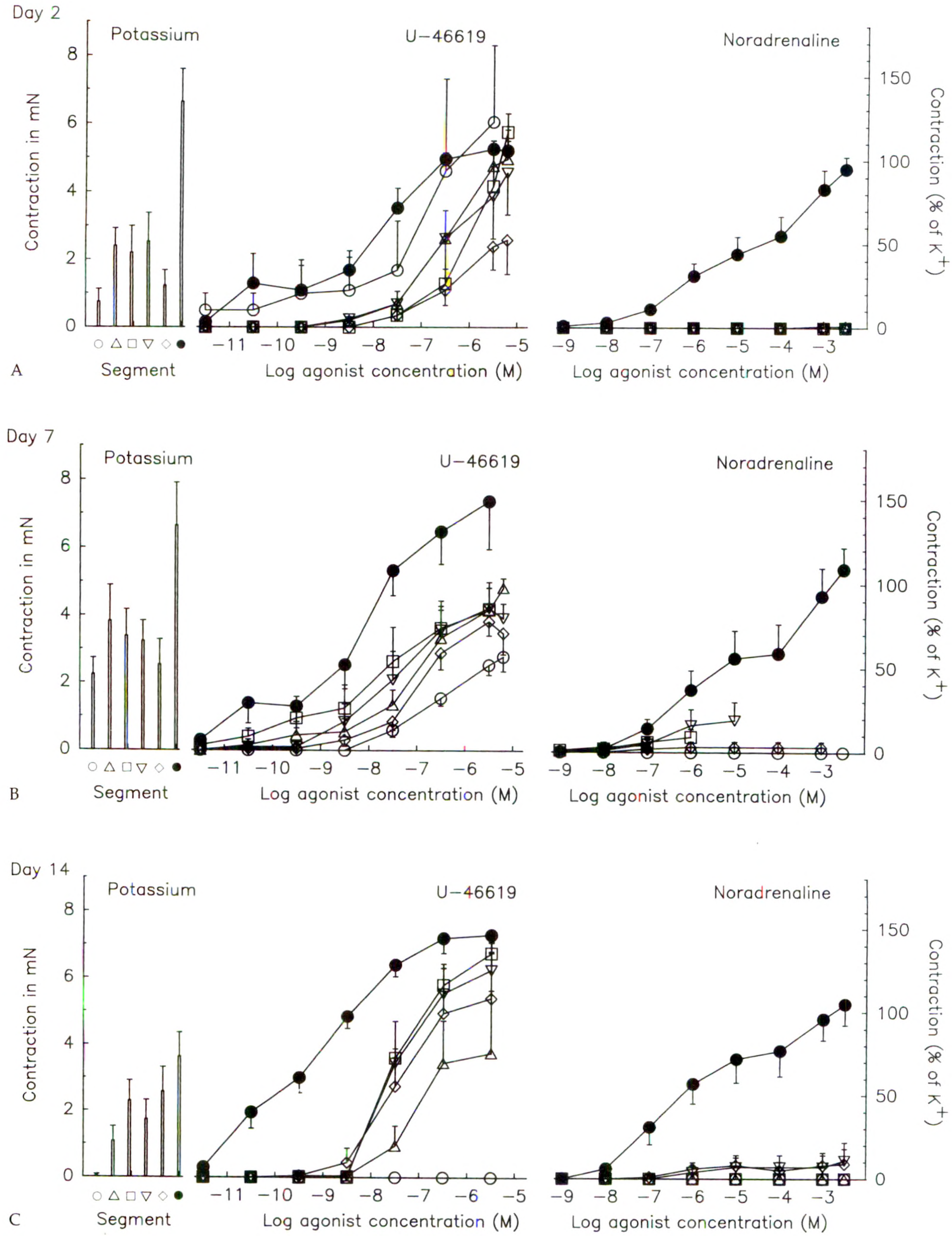

Fig 3. The contractile responses obtained in the free arterial graft and the control segments to K^+ (124 mmol/L), expressed in mN (left), and for U-46619 (middle) and noradrenaline (right), expressed as the percentage of the K^+-induced contraction. Each point in the curves indicates mean ± standard error of the mean. For number of segments, see Table 2. (○) segment 1, (△) segment 2, (□) segment 3, (▽) segment 4, (◇) segment 5, and (●) control.

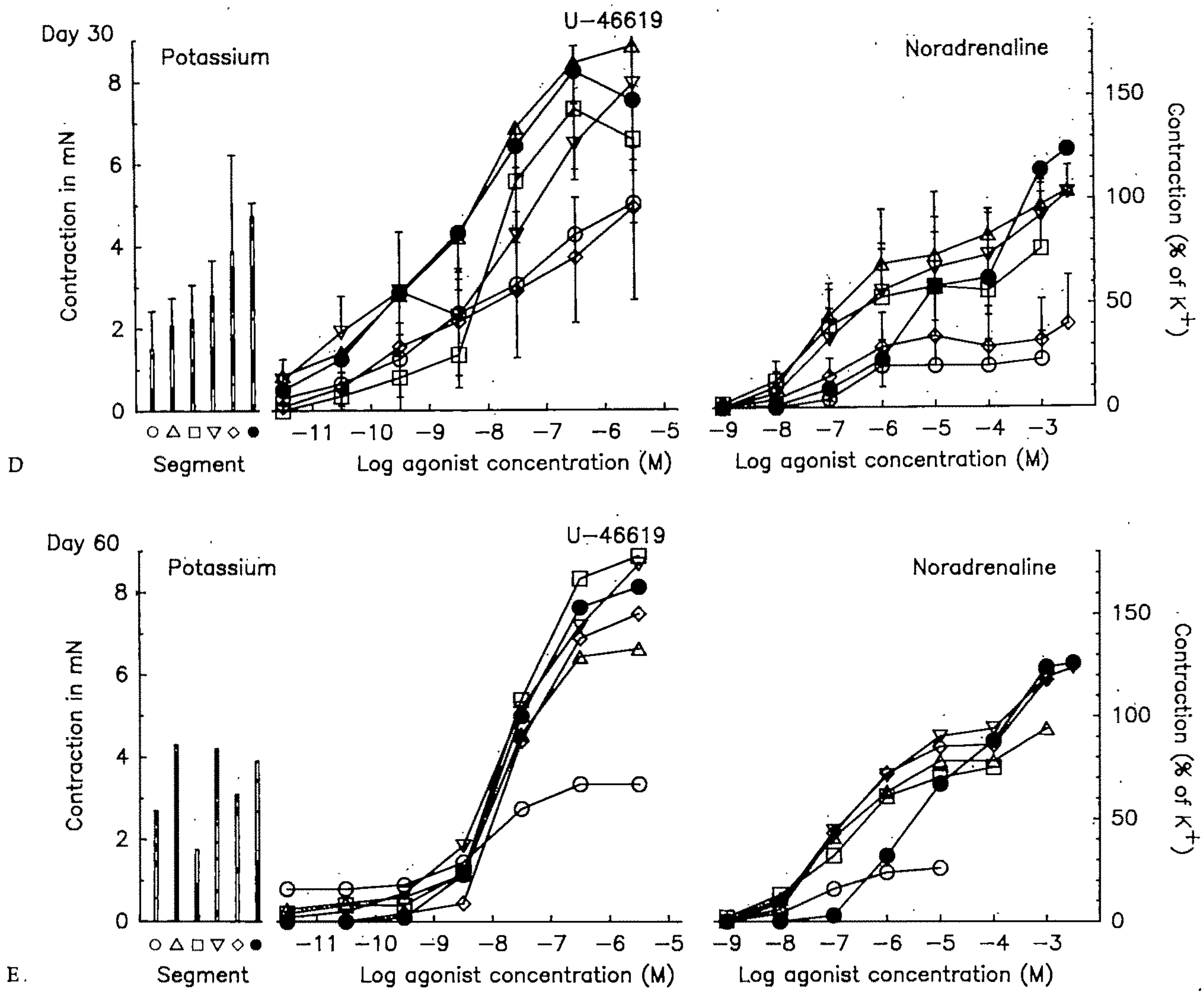

Fig 3. Continued.

anastomoses (segments 1 and 5) had lower contractile capacity than the other graft segments (see Fig 3).

Responses to the Thromboxane Analogue U-46619

U-46619 elicited contraction in all graft segments. When comparing the graft segment from each rat having the highest E_{max} value with the control segment, no significant differences were found at any time. When the corresponding pEC_{50} values were compared on day 2 they were significantly lower ($p < 0.01$) in the graft segments ($pEC_{50} = 6.6 \pm 0.3$) than in the controls ($pEC_{50} = 8.5 \pm 0.6$). The same relationship ($p < 0.05$) was found on day 14 ($pEC_{50} = 7.5 \pm 0.1$ and 9.3 ± 0.3, respectively). On day 7 and day ≥30 (ie, analyzing day 30 and 60 as one group to get a large enough sample for statistical evaluation) no significant differences were found.

Responses to Noradrenaline

Noradrenaline induced no or only weak contractions in the graft segments during the first 14 days, but at 30 and 60 days it elicited full contractile force in segments 2 through 4, ie, no significant difference existed between the E_{max} values in these graft segments as compared with the controls (see Fig 3). After 30 days noradrenaline was at most 80 times more potent in the graft segments as compared with the controls, and after 60 days it was at most 126 times more potent in the graft segments.

Putting together the segment from each rat with the highest contractile capacity on day 30 and 60, their pEC_{50} values (6.7 ± 0.3) were significantly greater ($p < 0.01$) than in the controls (4.9 ± 0.4). The relation between the EC_{50} concentrations was thus: $10^{-4.9}:10^{-6.7} = 10^{-4.9-(-6.7)} = 10^{+1.8} = 63$; ie, noradrenaline was 63 times more potent in the graft segments than in the control segments.

Comment

The potassium-rich (124 mmol/L) Krebs solution used in the present study creates a depolarization of the smooth muscle cell membrane; this elicits a constant activation of potential-operated calcium channels with subsequent entry of calcium into the myocytes, thus eliciting a contraction. When a steady state is reached, a stable, constant vasocontraction will be present. We used the amplitude of this contraction as an internal standard for each vessel segment studied, and expressed the responses obtained with the other drugs as a percentage of this maximal potassium-induced contraction. This is a generally accepted way of presenting vasoconstrictive effects, having the advantage that the responses of different drugs to different vessel segments can be compared independently of the sizes or muscle masses.

Radial artery grafts for aortocoronary bypass were used with early favorable results [4]. However, most of these grafts occluded within several months [5, 13]. Chiu [14] studied the histology of free femoral arterial and external jugular vein grafts in dogs after 60 days. Half of the grafts were wrapped with plastic sheets to interfere with the regeneration of vasa vasorum. As in the present study (see Fig 2F) he found mild to moderate subintimal hyperplasia in a number of the free femoral arterial grafts, particularly when the grafts were wrapped; the vein grafts had better patency and did not develop intimal hyperplasia except in one graft that was wrapped with the plastic sheet. Extrapolating these results to a clinical situation he suggested that free thick-walled, muscular arterial grafts with the vasa vasorum disrupted at both ends cannot regenerate readily from the adjacent tissue, as is the case in the aortocoronary bypass position, and therefore they are more vulnerable to subintimal hyperplasia and occlusion than thin-walled vein grafts. If his hypothesis is correct, the internal mammary artery, which is a thin-walled artery, should be better as a free aortocoronary bypass graft than the radial artery, which has a thicker wall. The observations of Loop and associates [7] suggest that this might be true, although the number of grafts studied was very small.

Our morphological results are in accordance with those of Chiu [14]. Furthermore, our findings indicate that hypercontractility, ie, increased sensitivity to cathecholamines (spasm), might be a problem in free arterial grafts because noradrenaline had full contractile force and was much more potent in the graft segments than in the controls after 30 and 60 days. One explanation of this increased potency of noradrenaline could be an upregulation of adrenergic α-adrenoceptors as a consequence of the total denervation of the free arterial graft.

Another explanation might be that the uptake of noradrenaline into sympathetic nerve endings, a physiological event, was abolished due to the lack of these nerves, and all the noradrenaline given was thus available to stimulate the postjunctional α-adrenergic receptors. During the first 14 days the α-adrenergic receptors seemed to be absent or out of function as noradrenaline had no contractile effect, whereas U-46619 had full contractile capacity in the same graft segments. After 1 month there was a hyperfunction of the α-adrenergic receptors because noradrenaline was significantly more potent in the grafts than in the controls. This might have contributed to the disappointing patency after 30 and 60 days, ie, circulating catecholamines, which under normal conditions should be unable to cause pathological vascular constriction, might now have induced spasm in the grafts resulting in occlusion.

The intimal thickening (see Fig 2D–F) that is generally seen in free muscular arterial grafts [14] might be another explanation of the poor patency. To our knowledge no study has been done to investigate if such a thickened intima is able to or has retained its normal capacity to produce relaxing or antithrombogenic factors. It has been shown that a regenerated endothelium has a reduced function of endothelium-derived relaxing factors [24]. To test these hypotheses a randomized study with and without a potent α-adrenergic antagonist should be done to asertain if an effective blockade of the α-adrenergic receptors would increase the patency of different free arterial grafts. Furthermore, corresponding studies should be done with, for example, antithrombotic or cytostatic drugs with the aim of preventing occlusion.

In conclusion, we think that a skeptical attitude to a liberal use of free arterial grafts in clinical surgery is warranted until more studies on this topic have been published.

We thank Prof Jan Kugelberg, our chief, who by his enthusiastic and economic support made this study possible.

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Coronary Bypass Grafting With Totally Calcified or Acutely Dissected Ascending Aorta

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From August 1984 through November 1988, 10 of 2,658 patients undergoing coronary artery bypass grafting had ascending aortic disease that was not amenable to proximal anastomoses for coronary bypass grafting. This was due to a calcified aorta in 6 and acute aortic dissection in 4. There were 5 male and 5 female patients with a mean age of 71 years. Cannulation site was the femoral artery in 5, ascending aorta in 3, and aortic arch in 2. Profound hypothermia and ventricular fibrillation, with no cross-clamp or cardioplegia, was used in 9 patients, and circulatory arrest in 1. In 8 patients a single internal mammary artery was used as the total inflow with a saphenous vein graft brought off the internal mammary artery to one or more distal left-sided coronary vessels. Bilateral internal mammary arteries were used in 2 other patients. Operative mortality was zero. There was one perioperative myocardial infarction and one transient stroke without sequelae. All patients have done well from 1 to 6 years postoperatively. These data support the use of internal mammary arteries as single or bilateral proximal conduits for other venoarterial bypass grafts when the aorta is extensively diseased either by calcification or dissection.

(Ann Thorac Surg 1991;51:102–4)

Cardiac operations performed on patients whose ascending aorta is difficult, either from calcification or dissection, are technically challenging and associated with a high morbidity. Stoney and associates [1] reported unexpected poor results in low-risk patients most frequently from manipulation of a diseased ascending aorta. With recognized disease of the ascending aorta and transverse aortic arch, cerebral injury has been shown to occur after cardiopulmonary bypass in more than 10% of patients [2].

We became interested in the operative management of the severely diseased aorta after Mills' [3] report on this subject as the age of our patient population began to rise and we saw a concomitant increase in postoperative stroke rate. We reviewed our experience with management of the difficult aorta in coronary artery bypass operations in which the ascending aorta was not used for any proximal anastomosis to determine the utility of this approach in terms of early and late morbidity.

Material and Methods

We analyzed the records of the 2,658 consecutive patients who underwent coronary artery bypass grafting at the Brigham and Women's Hospital from August 1984 through November 1988. In 10 (0.4%) of these patients the aorta was not used as the inflow portion for any conduit. There were 5 male and 5 female patients. The ages ranged from 65 to 78 years, with a mean of 71 years. In eight instances there was severe associated peripheral vascular disease—five in the femoropopliteal position and three in the carotids. In 6 patients, this was their first coronary artery bypass grafting; for 3 patients, this was their second operation for coronary artery bypass grafting; and in 1 patient, this operation followed a previous median sternotomy for attempted coronary artery bypass grafting which was aborted after the calcified aorta was palpated. In 6 patients, the wall of the ascending aorta was totally or near-totally calcified. In 4 patients, there was an acute aortic dissection: one iatrogenic, one iatrogenic from another hospital, and two spontaneous.

In all cases manipulation of the ascending aorta was avoided. The femoral artery was used for cannulation in 5 patients, an isolated "soft spot" very distal on the ascending aorta in 3 patients, and the lesser curvature of the transverse arch in 2 patients. In 8 patients, myocardial protection was provided by profound systemic hypothermia and ventricular fibrillation without cross-clamp or cardioplegia. In 1 patient with aortic dissection, profound systemic hypothermia was used along with cardioplegia, and in 1 patient it was necessary to employ circulatory arrest to replace a segment of distal ascending aorta where a dissection had occurred at the cannulation site.

The revascularization operations are summarized in Table 1. In 8 patients, a single internal mammary artery (IMA) was used as the inflow conduit for eight IMA-to-coronary artery anastomoses. To these eight IMAs, the greater saphenous vein was attached end-to-side, and then it was anastomosed to one or more distal coronary arteries for a total of ten distal anastomoses. The cephalic vein was used in a similar fashion to one distal coronary

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Table 1. Revascularization Operative Data

Patient No.	Sex	Age (y)	Associated Vascular Disease	Operation	Complications	Discharged
1	M	78	Femoropopliteal	RIMA–RCA, LIMA–LAD	. . .	Yes
2	M	66	. . .	LIMA–LAD, SVG–OMB	GI bleed	Yes
3	F	74	. . .	RIMA–LAD, CEPH–PDA	. . .	Yes
4	F	71	Carotid, femoropopliteal	LIMA–LAD, SVG–OMB–OMB	. . .	Yes
5	M	71	. . .	RIMA–RCA, SVG–OMB, LIMA–LAD	. . .	Yes
6	F	65	Carotid, femoropopliteal	RIMA–LAD, SVG–RCA	. . .	Yes
7	F	71	Femoropopliteal	LIMA–LAD, SVG–OMB	. . .	Yes
8	M	75	Carotid, femoropopliteal	LIMA–LAD, SVG–LADD$_1$–OMB$_1$	Frontal lobe stroke	Yes
9	F	65	. . .	LIMA–LAD, SVG–PDA	Subendocardial MI	Yes
10	M	70	. . .	LIMA–LAD, SVG–OMB$_1$–OMB$_2$	. . .	Yes

CEPH = cephalic vein; GI = gastrointestinal; LAD = left anterior descending artery; LADD$_1$ = first diagonal artery; LIMA = left internal mammary artery; MI = myocardial infarction; OMB$_1$ = first obtuse marginal artery; OMB$_2$ = second obtuse marginal artery; PDA = posterior descending artery; RCA = right coronary artery; RIMA = right internal mammary artery; SVG = saphenous vein graft.

artery. Internal mammary artery anastomoses were carried out with running 7-0 Prolene (Ethicon, Somerville, NJ) sutures.

In 2 patients, bilateral IMAs were used as the inflow conduit for four IMA-to-coronary artery anastomoses. The greater saphenous vein was attached end-to-side to one of these IMAs and anastomosed to one distal coronary artery (Fig 1). In 1 patient, no venous conduits were used at all. Complete revascularization was accomplished in 8 of 10 patients.

Results

Operative survival was 100%. There were two postoperative complications. A subendocardial myocardial infarction occurred in 1 patient with aortic dissection. There was also one small left frontal lobe stroke in a patient with a calcified aorta and bilateral carotid disease in whom no cross-clamp was used. His recovery after right arm weakness without residua was completed during his hospitalization.

Follow-up has ranged from 1 to 6 years, with a mean of 4 years. Nine patients are still alive and doing well. One patient died at 4 years postoperatively of unknown causes. There have been no reoperations.

Comment

The data suggest that the use of the IMA to provide total inflow for all bypass grafts in patients with totally calcified or acutely dissected ascending aortas, along with minimal other manipulation of the aorta, provides a safe solution to a potentially lethal technical problem that up to now has had no universally successful solution.

A number of techniques have been described for dealing with the diseased ascending aorta during coronary

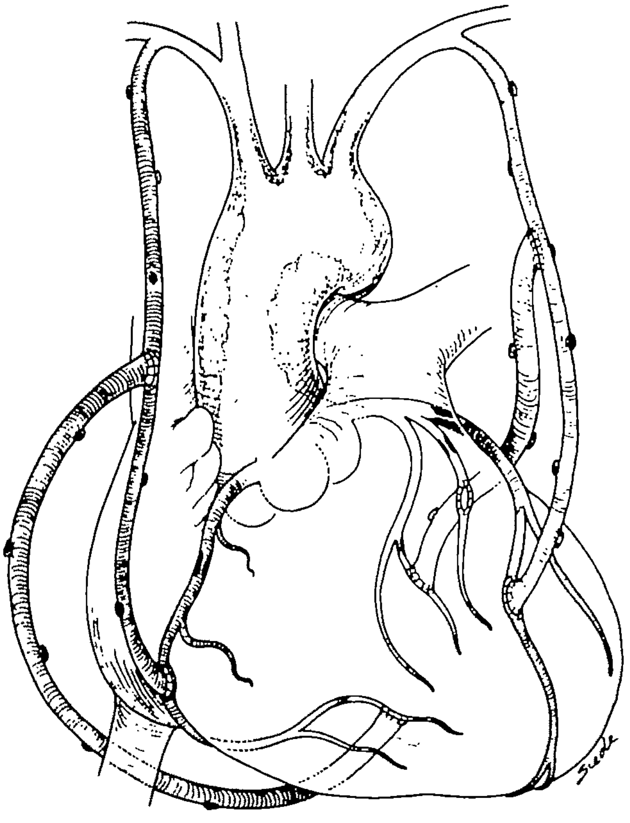

Fig 1. Bilateral internal mammary artery grafts may be used in conjunction with saphenous vein grafts when the ascending aorta is severely diseased. The saphenous vein grafts are anastomosed proximally to the proximal internal mammary artery end to side. (Reproduced with permission from: Mills N. Physiologic and technical aspects of internal mammary artery–coronary artery bypass grafts. In: Cohn LH, ed. Modern techniques in surgery: cardiac/thoracic surgery. Mt. Kisco, NY: Futura, 1982:48.17.)

artery bypass. Performing all coronary artery bypass grafts under one cross-clamp and avoiding a reapplication of a partial occlusion clamp for proximal anastomoses is a widely used technique. Robicsek and Rubenstein [4] described placing all proximal vein graft anastomoses onto a Teflon patch graft placed in a longitudinal aortotomy to avoid compromising the anastomoses. Culliford and associates [5] described an aggressive technique of circulatory arrest and then ascending aortic endarterectomy. Holland and Hieb [6] and Weinstein and Killen [7] have both individually reported using the innominate artery as the inflow portion for proximal vein graft anastomoses.

Murphy and Hatcher [8] reported extending the length of the IMA to reach the back of the heart by anastomosing end-to-end a piece of saphenous vein graft to the IMA. This allowed leaving the IMA in situ and avoidance of clamping the ascending aorta. Mills [3] was the first to describe attaching one to three saphenous vein grafts to the IMA to provide the total inflow for multiple coronary artery obstructions in this setting.

Mills and associates [9] have also tried to predict patients with the difficult aorta. At risk for having a difficult aorta are those patients with carotid or abdominal aortic disease and patients whose angiograms show aortic wall irregularity. Five of our 10 patients had clinically significant peripheral vascular disease. Though intraoperatively there are some physical signs of the calcified ascending aorta, transesophageal echocardiography may be the best way to diagnose this condition [9].

Is the IMA capable of supplying enough blood to provide total inflow for revascularization in this scenario? Dion [10] looked at this question in 531 IMA anastomoses that were performed in a sequential fashion. In the 319 patients that underwent thallium stress testing, there was no ischemia demonstrated in the region of the sequential IMAs at 6 months. Further, Hodgson and associates [11] looked at coronary flow reserve in patients with sequential IMAs by measuring reactive hyperemia using digital angiography and comparing basal flow with flow 10 to 15 seconds later, which reflects contrast-induced hyperemia. At postoperative day 25, there was no difference between coronary flow reserve at the proximal versus the distal sequential anastomosis. Further, there was no difference in the coronary flow reserve to the vascular bed distal to either a sequential IMA, a single IMA, a single saphenous vein graft, or a nonstenotic native coronary artery. Mills and associates [9] have also done exercise testing as well as postoperative angiography in many patients with only IMA inflow to multiple coronary arteries with excellent results. Five of our 10 patients have had postoperative stress testing and 2 others had "clinical" stress tests provided by gastrointestinal bleeding, and all demonstrated no myocardial ischemia.

In conclusion, these data support the use of the IMA to provide total inflow for all bypass grafts in patients with a totally calcified or acutely dissected ascending aorta. This method provides a satisfactory solution to a potentially lethal technical problem during coronary revascularization.

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Metabolism of the Heart and Brain During Hypothermic Cardiopulmonary Bypass

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The alterations in tissue metabolism induced by hypothermic cardiopulmonary bypass are not completely known. Phosphorus-31 nuclear magnetic resonance spectroscopy was used to determine the effect of hypothermic cardiopulmonary bypass on energy states and intracellular pH of the heart and brain. Sheep were instrumented for cardiopulmonary bypass and had a radiofrequency coil placed over either the heart or skull. The animals were placed in a 4.7-T magnet at 37°C and spectra obtained. The animals were cooled on cardiopulmonary bypass to either 26°C (n = 17) or 18°C (n = 14) for brain studies and to 26°C (n = 12) for heart studies. Hypothermia increased the phosphocreatine/adenosine triphosphate ratio in the heart (2.38 ± 0.23 versus 3.18 ± 0.37, 37° versus 26°C, respectively, $p = 0.03$). The brain phosphocreatine/adenosine triphosphate ratio increased from 1.70 ± 0.09 at 37°C to 2.00 ± 0.12 at 26°C ($p = 0.009$) and 2.10 ± 0.07 at 18°C ($p = 0.0001$). Intracellular pH increased during hypothermia (heart: 7.05 ± 0.02 to 7.18 ± 0.02, 37° versus 26°C, $p = 0.0001$; and brain: 7.07 ± 0.02 versus 7.32 ± 0.02, 37° versus 18°C, $p = 0.0001$). The adenosine triphosphate resonance position is known to be sensitive to magnesium binding as well as temperature and was shifted upfield ($p < 0.01$) in both the heart and brain. This effect could be totally explained by the temperature dependence of this process. It is concluded that deep hypothermia increases the energy state and the intracellular pH of both the heart and the brain. The elevated intracellular pH and the increase in tissue energy state may partially explain the beneficial effects of hypothermia on organ tolerance to ischemia.

(Ann Thorac Surg 1991;51:105–9)

Cardiopulmonary bypass (CPB) with moderate hypothermia is routinely used in cardiac surgical procedures for support of the circulation. Cardiopulmonary bypass also is used to induce deep hypothermia before circulatory arrest for operative procedures for congenital and acquired heart disease. Neurosurgical and thoracic vascular procedures commonly are aided by the use of hypothermic CPB and circulatory arrest. Cardiopulmonary bypass has been advocated after cardiac arrest to improve brain recovery [1].

There are few quantitative studies of the physiological and biochemical changes induced by hypothermic CPB. Hypothermia is known to modify the tissue response to ischemia. Knowledge of the metabolism and concentrations of high-energy phosphate compounds is necessary for evaluation of cerebral and myocardial physiology during hypothermia and ischemia. Phosphorus-31 nuclear magnetic resonance spectroscopy allows the nondestructive continuous measurement of high-energy phosphate concentrations and intracellular pH [2]. The objective of this study was to determine whether hypothermic CPB altered the metabolism of the heart and brain by increasing the energy state of these organs. An increase in high-energy phosphate levels would be expected to increase the tolerance to ischemia beyond the protection produced by the temperature-induced decrease in basal metabolic rate.

Material and Methods

Animal Preparation

All animal experiments were conducted with the approval of the NHLBI Animal Care and Use Committee in accordance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication 85-23, revised 1985). Forty-five sheep, greater than 8 weeks of age, weighing between 16 and 34 kg were used in this study. Hornless sheep were chosen for the brain study because of the relatively thin skull bones in the frontoparietal area. Adolescent sheep lack 2,3-diphosphoglycerate in the red blood cells, thus eliminating interference with detection of inorganic phosphate (Pi) [3].

The animals were divided into three groups. In the first group (n = 12), myocardial studies were performed during control (37°C) and on CPB at 26°C. A second group (n = 17) underwent brain studies at 37°C, then were cooled to 26°C on CPB. The final group (n = 14) had brain studies at 37°C and then after cooling to 18°C on CPB.

Anesthesia was induced with intravenous thiopental (20 mg/kg). Each animal was intubated and maintained on a nitrous oxide 20%/oxygen 80%/halothane 1% inhalation anesthetic. Pancuronium (0.1 mg/kg, intravenously) was given hourly for muscle paralysis. All animals were ven-

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tilated with a pediatric volume ventilator (D-900; Siemans-Allis, Cherry Hill, NJ).

Femoral arterial pressure and venous infusion catheters were placed in all animals. For the cerebral studies, the skin and subcutaneous tissue over the frontal and parietal regions of the skull were removed using electrocautery for hemostasis. An insulated two-turn radiofrequency coil, 2 cm in diameter, was secured with tape over the skull.

The sheep having myocardial studies had a left thoracotomy with removal of three or four ribs over the area of the myocardium. The pericardial fat pad was removed but the pericardium was not opened. The radiofrequency coil was secured to the pericardium with sutures over the apex of the left ventricle, thus allowing unrestricted cardiac motion. The chest cavity was sealed with cellophane to prevent heat and water loss. The lung was retracted and secured so as not to touch the coil. An atrial pacing lead was attached to the pericardium over the left atrium and the ground lead attached to the chest wall.

The animals were given sodium heparin (300 U/kg) and 12F to 14F femoral arterial and 24F jugular venous CPB cannulas were inserted. All animals had nasopharyngeal fiberoptic temperature transducers (Model 750; Luxtron, Mountain View, CA), which had previously been calibrated in the magnetic field. An inferior vena caval catheter with an incorporated thermistor for the determination of blood temperature was inserted through the femoral vein. The animals were wrapped in an insulating blanket and placed in a cradle to facilitate placement in the bore of the magnet. Cardiopulmonary bypass cannulas and pressure catheters were connected to the appropriate instrumentation by 4.5-m lengths of tubing. Arterial blood gases were measured intermittently by a Radiometer Model ABL3 blood gas analyzer. Arterial oxygen tension was maintained greater than 100 mm Hg and carbon dioxide tension ranged from 25 to 45 mm Hg during hypothermic CPB. Arterial pressure was measured using a Statham P23 pressure transducer connected to a Gould strip chart recorder. Mean arterial pressure was maintained between 60 and 90 mm Hg at 37°C and 40 to 50 mm Hg at 18°C.

Cardiopulmonary Bypass

The cardiopulmonary bypass circuit consisted of a Bio-Medicus (Model BP80; Bio-Medicus, Minneapolis, MN) centrifugal pump, a 33-μm arterial filter (H-625; Bard, Billerica, MA), and a membrane oxygenator (Capiox 4.3 m^2; Terumo, Piscattaway, NJ) with integral heat exchanger. Blood gases were measured inline (System 200, Cardiovascular Devices). The Bio-Medicus pump and its electromagnetic flowmeter remained 4.5 m from the magnet and performed normally in the magnetic field (approximately 15 G) present at this distance. The circuit was primed with 2,400 mL of lactated Ringers' solution containing 5% dextrose, 10,000 U of heparin, 44 mg of sodium bicarbonate, and 50 mg of 2% lidocaine (to prevent ventricular fibrillation during cooling). Blood flows were maintained between 60 and 100 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} during CPB. A cardiotomy reservoir was placed in the venous side of the circuit, which permitted the rapid administration of fluid during cardiopulmonary bypass. Control spectra at 37°C off CPB were collected. Cardiopulmonary bypass was instituted and the animals were cooled to 26°C over a 30- to 60-minute interval for the moderate hypothermia studies of the heart and brain. Additional sheep (n = 14) were cooled to 18°C for the deep hypothermia brain studies. After stabilization for approximately 30 minutes, final spectra were collected.

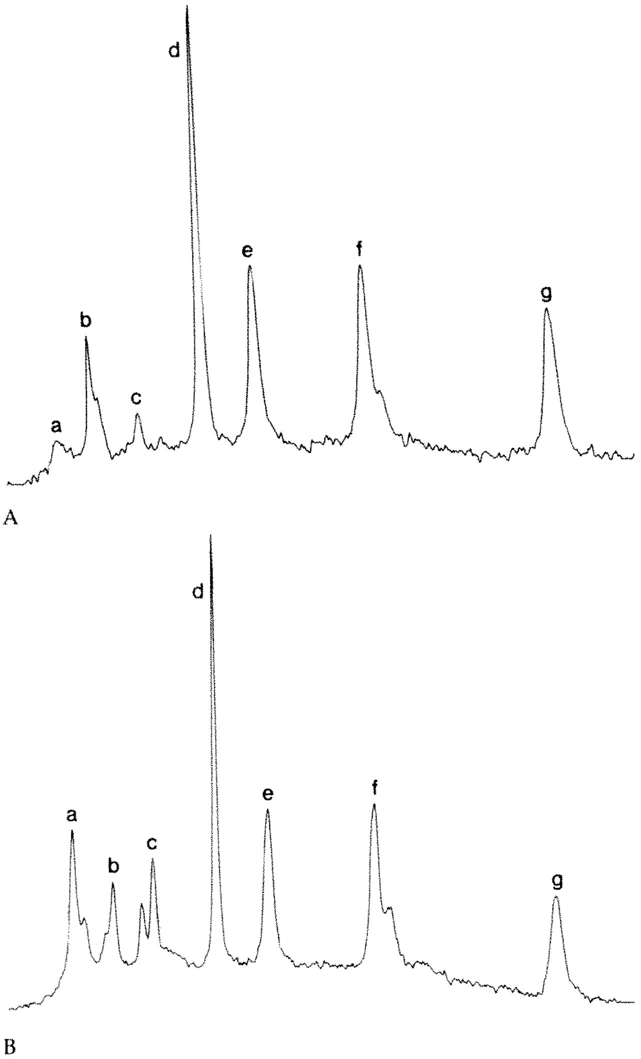

Fig 1. Typical heart (A) and brain (B) spectra from a sheep at 37°C before cardiopulmonary bypass. Peak assignments are: (a) monophosphates, (b) inorganic phosphate, (c) diphosphates, (d) phosphocreatine, (e) γ-adenosine triphosphate (ATP), (f) α-ATP, and (g) β-ATP. (Spectra represent 400 acquisitions and are processed with 10 Hz of line broadening.)

Nuclear Magnetic Resonance Spectroscopy

The animals were positioned so either the brain or the heart was in the center of the bore of an Oxford Instruments 4.7-T magnet. Nuclear magnetic resonance data were collected with a General Electric CSI spectrometer. Phosphorus-31 nuclear magnetic resonance spectroscopy of the brain was performed with a pulse program de-

Table 1. Effect of Hypothermia on Heart and Brain Metabolism[a]

Organ	PCr/ATP[b]	ATP/Pi	PCr/Pi	β-ATP Peak Position (ppm)	pHi
Heart (n = 12)					
37°C	2.38 ± 0.23	2.04 ± 0.37	3.38 ± 0.48	−16.08 ± 0.02	7.05 ± 0.02
26°C	3.18 ± 0.37[c]	2.19 ± 0.40	5.60 ± 0.97	−16.17 ± 0.02[d]	7.18 ± 0.02[d]
Brain (n = 17)					
37°C	1.70 ± 0.09	1.74 ± 0.57	1.89 ± 0.12	−16.30 ± 0.03	7.05 ± 0.01
26°C	2.00 ± 0.12[d]	1.85 ± 0.15	2.40 ± 0.21[c]	−16.43 ± 0.02[d]	7.26 ± 0.01[d]
Brain (n = 14)					
37°C	1.74 ± 0.07	1.91 ± 0.15	2.24 ± 0.15	−16.25 ± 0.02	7.07 ± 0.02
18°C	2.10 ± 0.07[d]	2.37 ± 0.27[c]	3.23 ± 0.30[d]	−16.44 ± 0.02[d]	7.32 ± 0.02[d]

[a] All values are mean ± standard error of the mean. [b] PCr/ATP values are corrected for spin-lattice relaxation time saturation effects. [c] $p < 0.05$. [d] $p < 0.01$.

ATP = adenosine triphosphate; pHi = intracellular pH; Pi = inorganic phosphate; PCr = phosphocreatine.

signed to minimize the contribution of bone to the signal [4]. Respiratory and cardiac gating was performed for shimming and data acquisition for the heart experiments [5].

Data were collected in 400 acquisition (20-minute) blocks. The spectra were analyzed using the GEMCAP Lorentzian line-fitting program, a part of the GEMCSI software. Peak positions were characterized as parts per million spectral shift from phosphocreatine (PCr). The spectral shift of Pi had been previously calibrated to both pH and temperature [4] and these calibrations were used to calculate intracellular pH in this study.

The spin-lattice relaxation times of the heart [6] and brain [7] have been measured previously in our laboratory and reported. No significant temperature-dependent differences were found in the spin-lattice relaxation time values in the temperature range used in this study. The spin-lattice relaxation time values (and the calculated saturation correction factors in parentheses) for the brain are: PCr, 4.73 s (0.56); β-adenosine triphosphate (ATP), 1.51 s (0.84); and Pi, 3.36 s (0.64), thus resulting in a PCr/ATP correction factor of 1.50. The values for the heart are: β-ATP, 1.55 s (0.82), and PCr, 4.15 s (0.58). Previous data [6] from spin-lattice relaxation time calculations from fully relaxed spectra were averaged with the above heart data and a correction factor of 1.35 for the PCr/ATP ratio was used for the present experiments. The PCR/Pi and ATP/Pi ratios were uncorrected for saturation.

The relatively lower concentration of Pi, as compared with ATP and PCr, and the overlapping resonances in the 2- to 8-ppm region make quantitation of Pi difficult and result in larger errors in measurement (as reflected in the greater standard errors of the ATP/Pi and PCr/Pi ratios when compared with PCr/ATP).

Statistical Analysis

Results were expressed as the mean value ± the standard error of the mean. Statistical significance (to the 95% confidence level) was determined using the Excel Statmac macro statistical program using the paired Student's *t* test for comparisons of the effect of temperature on the variables for each animal at control and during hypothermic CPB.

Results

Typical spectra from the experiments on the heart and brain (Fig 1) are shown. Results are summarized in Table 1 and Figure 2.

Hypothermia resulted in an upfield shift in the resonance frequency (as compared with PCr) of the β-ATP peak. Hypothermic CPB significantly increased the PCr/ATP ratios in the heart by 38% at 26°C and by 21% and 23% in the brain at 26°C and 18°C, respectively. The PCr/Pi ratio in the brain was significantly increased at 26°C and at 18°C. Although the PCr/Pi ratio was greater during hypothermia in the heart, the increase did not achieve significance ($p = 0.06$). The ATP/Pi ratio in the brain was significantly increased at 18°C ($p = 0.04$). This ratio increased in both the heart and brain at 26°C, but the changes did not achieve significance. The intracellular pH of the heart and brain increased as temperature decreased (see Table 1).

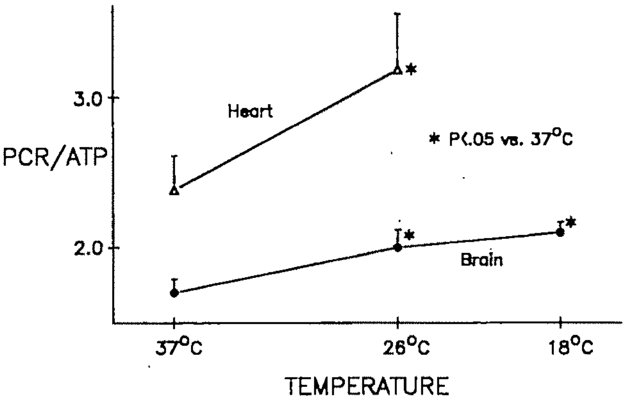

Fig 2. Plot of phosphocreatine/adenosine triphosphate (PCR/ATP) ratio versus temperature for heart and brain spectra during hypothermia.

Comment

The biochemical processes associated with hypothermia in the heart and brain have not been fully elucidated. Because moderate (25° to 32°C) hypothermia is used during most cardiac surgical operations and deep hypothermia (<20°C) is induced before circulatory arrest, an understanding of the changes in the metabolism of heart and brain tissue may be important in the choice of the degree of hypothermia.

The mechanisms of the protective effects of hypothermia on tissue are not completely known. Metabolic measurements of the reduction in oxygen consumption during deep hypothermia [8] do not fully explain the increase in tolerance to cerebral ischemia produced by hypothermia [9, 10]. Oxygen consumption is decreased approximately 5% per degree Centigrade between 37° and 22°C [11] and is one fifth that of normothermia at 20°C [10, 12], whereas the tolerance to ischemia is increased up to 30 times at this temperature [13, 14]. The results of the present study suggest some of the protective effects of hypothermia might be related to an increase in the energy state of the tissues, an increase in intracellular pH, and possible changes in Mg^{2+}-dependent enzyme activity.

The use of CPB to induce hypothermia may exert a protective effect by supporting the circulation to ensure normal perfusion and oxygen delivery while oxygen consumption decreases owing to hypothermia. Fox and associates [12] have shown that brain oxygen consumption decreases with hypothermia and is independent of CPB flow rate for a wide range of flows (0.25 to 1.5 $L \cdot min^{-1} \cdot m^{-2}$). In the heart, CPB has the added effect of decreasing myocardial oxygen consumption by decreasing preload and lowering wall tension, coupled with bradycardia. However, the decrease in myocardial work does not in itself increase the myocardial energy state because normothermic CPB does not increase the basal energy state of the heart or brain [7].

The present study demonstrates that the ratios of ATP/Pi and PCr/Pi in the heart and brain are significantly increased with hypothermic CPB. The following equations describe high-energy phosphate relations in the cell (ADP = adenosine diphosphate):

$$\mathrm{ATP} + \mathrm{H_2O} \leftrightharpoons \mathrm{ADP} + \mathrm{Pi} + \mathrm{H}^+ \qquad (1)$$

$$\mathrm{PCr} + \mathrm{ADP} + \mathrm{H}^+ \leftrightharpoons \mathrm{creatine} + \mathrm{ATP} \qquad (2)$$

The phosphorylation potential (a measure of the energy state of the cell) is defined as:

$$\mathrm{PP} = \frac{[\mathrm{ATP}]}{[\mathrm{ADP}]\,[\mathrm{Pi}]} = \frac{[\mathrm{PCr}]}{[\mathrm{Pi}]} \times \frac{c\,[\mathrm{H}^+]}{[\mathrm{creatine}]} \qquad (3)$$

During steady-state conditions, c (the creatine kinase equilibrium constant), the pH, and the concentration of creatine are constant. Therefore, the phosphorylation potential is proportional to the ratio PCr/Pi. As can be seen from the above equations, the PCr/ATP ratio is inversely proportional to ADP concentration and is a reflection of energy state, as is the ATP/Pi ratio. The data demonstrate that hypothermia increases high-energy phosphate levels in the heart and brain.

This net increase in high-energy phosphates (ie, increase in PCr and decrease in ADP and Pi) could be the result of two processes: (1) a relative decrease in ATPase activity versus ATP synthesis (via glycolysis or oxidative phosphorylation) at low temperature or (2) a change in the equilibrium constant of the creatine kinase reaction at low temperature as well as the shift in the equilibrium due to the lower proton concentration (equation 2). No information is available on the temperature dependence of the creatine kinase equilibrium. Despite the actual mechanism for the change in high-energy phosphates, the net effect of lowering temperature is to increase the overall phosphorylation potential (equation 3) of the cell.

The present study found that hypothermia resulted in an upfield shift of the resonance frequency of ATP. It is known that ATP resonance shifts are produced by binding to divalent metal ions (Mg^{2+} and Ca^{2+}). However, a significant (0.012 ppm/degree Centigrade) shift also occurs with temperature alone [15]. Using this relationship, we found that the chemical shift of β-ATP during hypothermia could be completely explained by the change in temperature alone and is not due to changes in intracellular Mg^{2+}.

Finally, the finding of increased intracellular pH in the heart and brain during hypothermia may be another factor that may increase the protective effects of hypothermia during ischemia. Acidosis leads to many deleterious effects on enzyme function, ion permeability, and cellular function [16–18]. Therefore, hypothermia, by increasing intracellular pH, may delay irreversible tissue necrosis. This mechanism has been hypothesized as occurring when severed limbs are cooled before reimplantation [19]. In addition, it has been hypothesized that use of hypothermic CPB after cerebral ischemia secondary to cardiac arrest may improve neurological recovery by raising intracellular pH [1].

In conclusion, the present investigation was undertaken to determine changes in tissue energy state and intracellular pH with hypothermia. Hypothermia significantly increased the energy state and intracellular pH in both heart and brain, which may partially explain the beneficial effects of hypothermia on organ tolerance to ischemia. These beneficial effects of hypothermia on organ tolerance to ischemia may provide a rationale for the use of hypothermic CPB concomitant with high-risk angioplasty or after cardiac arrest to improve neurological recovery.

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Rupture of a Benign Mediastinal Teratoma Into the Right Pleural Cavity

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A 27-year-old woman with a ruptured mediastinal cystic teratoma had high levels of amylase and carcinoembryonic antigen in cystic fluid. The activity of the amylase is thought to be the most likely cause of the rupture. High levels of carcinoembryonic antigen in pleural fluid are not necessarily indicative of a malignant lesion but may suggest the presence of a ruptured teratoma in patients with mediastinal tumors.

(Ann Thorac Surg 1991;51:110–2)

The rupture into the pleural cavity of a benign cystic teratoma of the mediastinum is a rare complication. There are few reports of such a rupture [1], and we report here an additional case.

A 27-year-old woman was admitted to a neighboring hospital on August 7, 1986, because of the sudden onset of severe right-sided chest pain and shortness of breath. The roentgenogram demonstrated an extensive collection of pleural fluid on the right side. The patient's symptoms were improved after removal of fluid. However, subsequent chest roentgenograms showed a large, anterior mediastinal tumor (Fig 1) and the patient was transported to our hospital on August 24.

On physical examination, abnormal findings were confined to the right chest, which was dull on percussion; breath sounds were decreased but respirations were not labored. The hematocrit was 0.30, but other laboratory findings, including tumor markers, were all unremarkable. Computed tomography of the chest revealed a cystic mediastinal tumor, in which a nonhomogeneous rounded mass was present (Fig 2). Cytologic and microbiological studies of a sample of pleural fluid were negative. The sample contained 116 IU/L of amylase and 160 μg/L of carcinoembryonic antigen (CEA).

The preoperative diagnosis was a benign cystic teratoma that had ruptured into the right pleural cavity. A right thoracotomy was performed on November 4. The pleura was generally edematous and moderately thickened. A large cystic tumor, measuring 9 × 7 × 12 cm, lay in the anterior mediastinum and the right lung was dislocated posteriorly. The tumor was firmly attached to the innominate vein and the thymus. After removal of 200 mL of fluid from the tumor, dissection of the tumor was completed. The point of rupture was not obvious. The patient made an uneventful recovery from the operation.

The wall of the cyst was made up of fibrous tissue 2 to 5 mm thick, and there were some short hairs on its surface. The rounded mass in the cyst was 2.4 × 1.7 cm in size and made up of fatty tissue. Microscopic examination revealed that the inner surface of the cyst was lined with stratified squamous epithelium. The cyst wall contained tissues derived from all three germinal layers, as in skin appendages, cartilage, intestinal ducts, and salivary gland. There was no evidence of malignancy. The pathological diagnosis was matured teratoma. Some sections were examined by indirect immunoperoxidase staining for amylase and CEA. Positive staining for amylase was visible in the acinar cells of the salivary gland (Fig 3). Positive staining for CEA was apparent in the ductal epithelium of the salivary gland (Fig 4) and in some portions of the stratified squamous epithelium. Examination of the cystic fluid revealed that it contained 813 IU/L

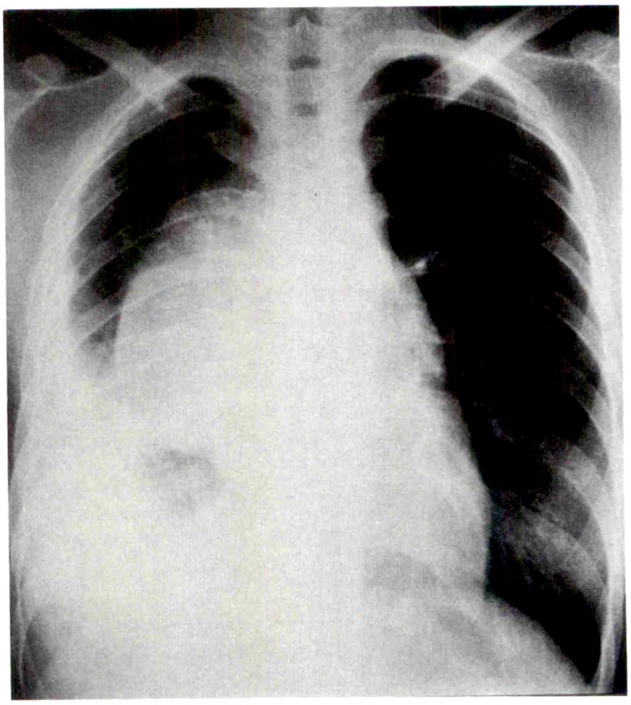

Fig 1. Chest roentgenogram showing an anterior mediastinal tumor.

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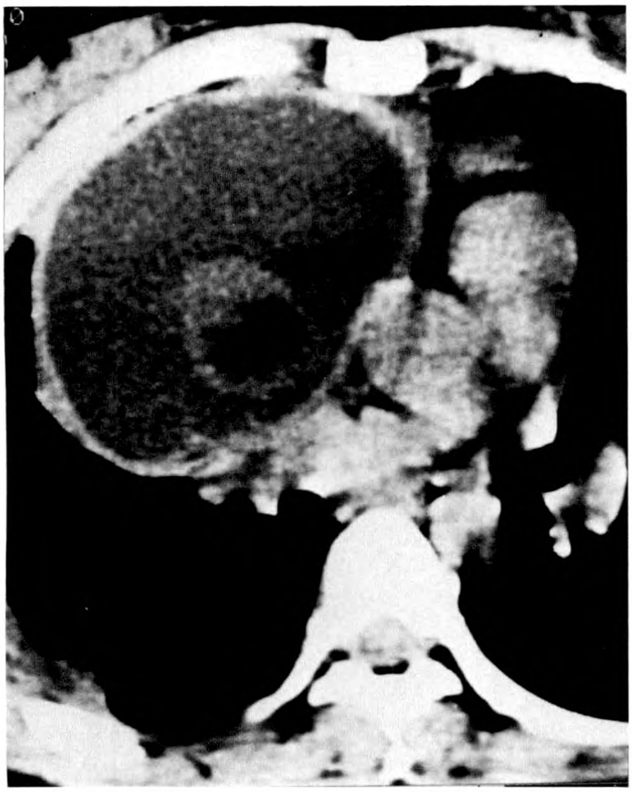

Fig 2. Computed tomography of the chest confirming a cystic mediastinal tumor with a rounded mass in it.

of amylase and 480 μg/L of CEA. The fluid was sterile on culture.

Comment

Several explanations have been given for the tendency to rupture of mediastinal teratomas. For example, enlargement of the tumor may result in ischemia, necrosis of the tumor, and then rupture. Infection has also been suggested as the cause of rupture. It has also been proposed that the sebaceous materials or digestive enzymes derived from the tumor tissues cause inflammation and necrosis, which result in rupture [2, 3]. Sommerlad and associates [4] and Southgate and Slade [5] reported cases of nonruptured cystic mediastinal teratoma in which they detected very high amylase activity in cystic fluid. Sommerlad and associates [4] proposed that digestive enzymes derived from the tumor might cause expansion and rupture of the tumor itself. Southgate and Slade [5] suggested that the tendency of a mediastinal teratoma to adhere to and erode surrounding structures was attributed to proteolytic enzymes produced in the tumor. In our patient, the level of amylase in pleural fluid was not elevated, but it was substantially elevated in cystic fluid. Immunohistochemical study demonstrated that amylase was produced by salivary glandular tissue of the tumor. The disparity between the levels of amylase in both fluids probably occurred because the metabolic clearance of amylase in pleural fluid was very rapid [6]. The tumor was not complicated by infection. In the present case, it is reasonable to suppose that amylase played an important role in rupture.

In the present case, although there was no evidence of malignancy, levels of CEA were elevated in samples of pleural fluid and cystic fluid. Immunohistochemical examination demonstrated CEA in the salivary glandular tissues of the tumor. Itoh and co-workers [3] also reported that although serum levels of CEA were not elevated, as in our patient, both pleural fluid and cystic fluid contained elevated levels of CEA, and immunohistochemical staining demonstrated CEA in the bronchial epithelium of a mediastinal benign teratoma. Because CEA is cleared more slowly from pleural fluid than from plasma [7], CEA level in pleural fluid was kept high, but not higher than

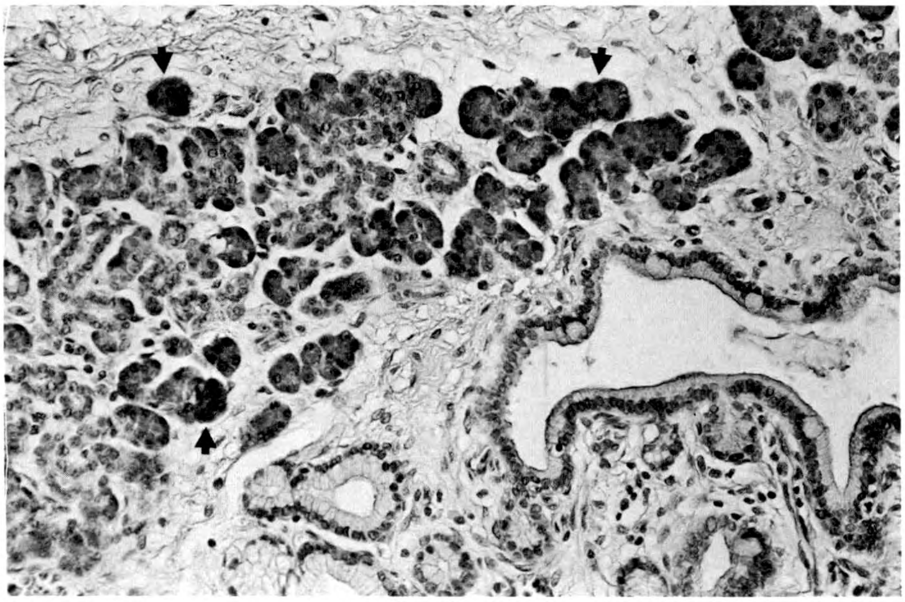

Fig 3. Positive staining for amylase is seen in the acinar cells of the salivary gland (arrows). *(Immunoperoxidase, ×200 before 42% reduction.)*

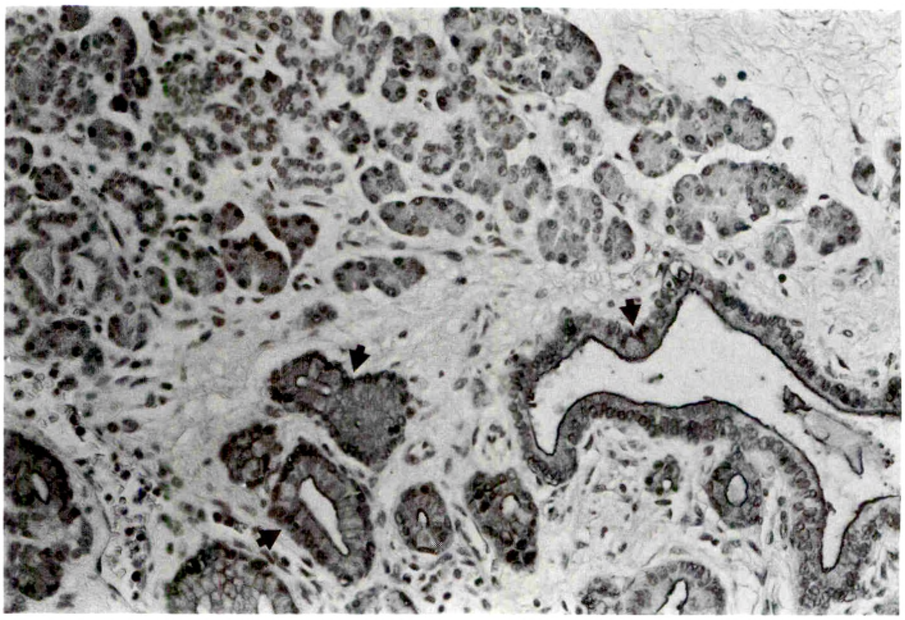

Fig 4. Positive staining for carcinoembryonic antigen is visible in the ductal epithelium of the salivary gland (arrows). *(Immunoperoxidase, ×200 before 42% reduction.)*

the level in cystic fluid in the case of teratoma. Shousha and Miller [8] reported a case of testicular malignant teratoma in which they detected CEA as well as α-fetoprotein and human chorionic gonadotropin. They suggested that measurements of levels of CEA might be useful because such levels might reflect the degree of teratomatous differentiation in nonseminomatous germ-cell tumors. Therefore, elevated levels of CEA in pleural fluid or cystic fluid are not necessarily indicative of malignancy but may suggest the presence of teratomatous elements in cases of mediastinal tumors.

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Penetrating Trauma Involving the Innominate Artery

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Penetrating trauma involving the innominate artery is uncommon. Few surgeons have experience with this injury. A successfully managed case of penetrating innominate artery trauma is summarized and the literature reviewed.

(Ann Thorac Surg 1991;51:113–5)

After reviewing four military series and 13 civilian series, Rich observed "probably less than 20 successful repairs of acute injuries to the intrathoracic great vessels have been reported in the English literature" [1]. Reported experience with penetrating innominate artery trauma is rare. Reported here is a successful technique for the management of penetrating innominate artery trauma.

A 28-year-old woman sustained a single gunshot wound to the chest. The entrance wound was located just above the sternal notch. The exit wound was located in the right back. The patient was never in shock, had no neurological deficit, and had equal pulses bilaterally. Angiography demonstrated a pseudoaneurysm of the innominate artery (Fig 1). The patient was taken to the operating room directly and explored through a sternal splitting incision. When the mediastinum was entered surprisingly little evidence of trauma was present. Observing this, we heparinized the patient. The extent of the injury necessitated proximal control of the innominate artery be obtained intrapericardially. Distal control was obtained by individually controlling the right subclavian and right carotid arteries. When the pseudoaneurysm was opened, the distal two thirds of the innominate artery was seen to be destroyed by the oblique passage of the bullet. Vascular continuity was obtained by the insertion of a properly sized Dacron bifurcation graft. The only other injury present was a through and through nonbleeding injury to the right upper lobe managed by chest tube placement.

Postoperatively, the patient did well. A neurological deficit was not noted. At early follow-up blood pressure in both arms is equal.

Comment

The true incidence of innominate artery injury is unknown, as the majority of patients exsanguinate before receiving treatment [2]. Bladergroen and associates [3] reported that 6 of 10 patients died before receiving a physician's attention. A previous compilation of the literature revealed only 13 cases of penetrating innominate artery trauma [1]. In addition to our patient we could only identify an additional 19 cases of innominate artery injuries from the literature (Table 1). Data are incomplete because innominate artery trauma was placed into larger series of thoracic vascular trauma.

Laceration of the vessel is the most frequently encountered lesion [1, 2]. Gunshot wounds rather than knife wounds appear to be the most frequent cause of penetrating innominate artery injury [4, 8, 9].

When first seen, most patients surviving to receive medical attention appear to have, like our patient, a paucity of external changes to indicate the magnitude of the injury. In the majority of patients the diagnosis is made when an arteriogram demonstrates a contained pseudoaneurysm [3–7]. Although Graham and associates [6] noted that all of their patients had associated subclavian vascular trauma, most authors fail to comment on the presence of associated injuries.

Once the diagnosis is made, the patient should be taken to the operating room. Median sternotomy offers excellent exposure of the innominate artery [3–6]; the safety of this incision makes it the preferred approach to the innominate artery. The patient and room should be kept as warm as possible. Intraoperative autotransfusion and use of a Cell Saver may be useful. Heparin use is controversial. Some authors [7] recommend its frequent employment. Mattox [10] has observed that in thoracic vascular trauma heparin is probably not indicated. Cardiopulmonary bypass does not appear to have been employed in any case of penetrating innominate artery trauma in the literature.

The general principles of adequate exposure with proximal and distal control of the innominate artery are followed. When the pseudoaneurysm is open, the lesion is repaired by the simplest means possible. In many instances this can be accomplished by debridement and primary repair [3, 7]. In some cases a saphenous vein patch or interposition graft will suffice [9]. However, for difficult or complex cases, a Dacron prosthetic graft may be the ideal solution. In our patient, employment of a bifurcation graft allowed for a simple reconstruction of the confluence of the innominate, right subclavian, and right

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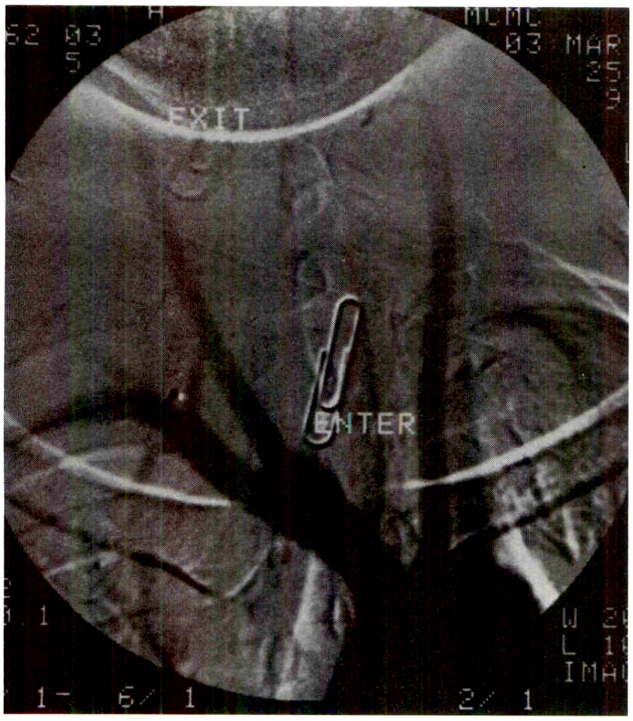

Fig 1. This subtraction arteriogram demonstrates how subtle a pseudoaneurysm of the innominate artery may be.

common carotid arteries without tension, stenosis, or kinking. This technique has previously been reported [11].

The postoperative morbidity and mortality of innominate artery injury cannot be accurately determined from the literature. However, there have been no reports of postoperative neurological deficits.

In conclusion, review of the literature reveals only 33 explorations for penetrating injuries to the innominate artery. The majority of patients with this injury die before reaching medical attention. Those surviving generally have an acute pseudoaneurysm of the innominate artery and minimal external signs of trauma. Usually repair is accomplished primarily or with saphenous vein graft. In difficult situations use of a Dacron bifurcation graft may be warranted.

Table 1. Innominate Artery Injuries

Author	Year	No. Cases	No. Survived	Years Reviewed
Lim et al [4]	1979	2	2	5
Pate and Casini [5]	1980	2	. . .[a]	25
Graham et al [6]	1980	7	. . .[a]	23
Bladergroen et al [4]	1989	4	. . .[a]	12
Weaver et al [7]	1989	4	4	10

[a] Insufficient data to determine survival.

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INVITED COMMENTARY

It is increasingly important that the thoracic surgeon remain current in the management of thoracic trauma. The development of trauma systems with rapid communication, triage, and transportation presents the surgeon with the responsibility to manage patients who would have died before arrival at the hospital in years past. Although penetrating injury to the innominate artery is unusual, our Trauma Center has managed 4 such patients from among 15,936 major trauma admissions within the last 5 years. The risk of cerebral ischemia and major neurological deficit is present in all injuries of aortic arch branches, and raises additional legal problems.

This report well summarizes the present knowledge of penetrating injury to the innominate artery. The authors' recommendations for immediate arteriography, emergency median sternotomy, proximal and distal vascular control before entering the hematoma, and encouragement for the use of prosthetic grafts delineate the major principles involved. We routinely open the pericardium for a proximal bypass graft and expose the common carotid in mid-neck for the distal graft end *before* we disturb the hematoma and area of injury. Both Dacron and Gore-Tex have been used; the only major difficulty with either has been in preventing kinking. I think a saphenous vein graft is too small and prone to late aneurysm formation in this location; therefore, we always use a prosthesis when primary repair is impractical. The advisability of heparin administration is unproven. We do use heparin for penetrating injuries of the carotid and innominate arteries, although usually not in blunt trauma to major systems.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 16, 1992. The closing date for registration is August 1, 1991.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Tricuspid Valve Papillary Fibroelastoma: Echocardiographic Characterization

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Sections of Pathology, Cardiovascular and Thoracic Surgery, Cardiovascular Diseases, and Rheumatology, Mayo Clinic Jacksonville, Jacksonville, Florida

We report a tricuspid valve papillary fibroelastoma initially detected by transthoracic two-dimensional echocardiography and subsequently characterized by transesophageal two-dimensional echocardiography. The mass was excised during open heart operation, and the diagnosis was verified grossly and histopathologically. Transesophageal echocardiography usually provides images far superior to those from transthoracic echocardiography and may be a useful adjunct for intraoperative localization of intracardiac tumors for excision.

(Ann Thorac Surg 1991;51:116–8)

Papillary fibroelastoma (PFE) is one of the most common benign primary heart tumors after myxoma [1]. Although usually an asymptomatic incidental finding at autopsy or operation, PFEs occasionally have been associated with transient ischemic attacks, cerebral infarctions, chest pain, or sudden death attributed to occlusion of coronary ostia [1]. Within the last decade, PFEs have been detected echocardiographically in fewer than 20 patients; only two PFEs were related to the tricuspid valve [2, 3]. We are aware of only two PFEs studied by transesophageal two-dimensional echocardiography, and neither was associated with the tricuspid valve [4, 5].

A 75-year-old woman was examined after a recently resolved left hemiparesis affecting principally her left hand. She had had cerebral ischemic attacks for at least 15 years. A brain scan showed multiple old bilateral cerebral infarcts. A diagnosis of systemic lupus erythematosus was made on the basis of positive serologic tests for antinuclear antibody, anti–double-stranded DNA antibody, anticardiolipin antibody (immunoglobulin G 1:4; immunoglobulin M negative), and rheumatoid factor, low concentration of third component of complement, increased erythrocyte sedimentation rate, grade 1 proteinuria, nonerosive polyarthritis, and Raynaud's phenomenon.

A two-dimensional echocardiogram showed a large pedunculated right ventricular mass, apparently associated with the septal leaflet of the tricuspid valve, that prolapsed into the right atrium during systole. There was also mild mitral and aortic regurgitation but no evidence of left-sided masses or intracardiac shunting.

A transesophageal two-dimensional echocardiogram demonstrated a 2.7-cm-diameter mass that had at least two lobes and was attached just beneath the septal leaflet of the tricuspid valve (Fig 1). The mass prolapsed into the right atrium in systole. Left heart catheterization and coronary angiography demonstrated normal left ventricular wall motion, mild mitral regurgitation, and a clinically significant flow-limiting lesion in the mid-right coronary artery.

At operation, a polypoid mass attached to the closing edge of the septal leaflet of the tricuspid valve was removed in two pieces without injuring the leaflet. A right coronary artery saphenous vein bypass graft was then performed.

Grossly, the neoplasm resembled a sea anemone and was composed of many fronds with minute filiform surface projections (Fig 2A). Microscopically, there were several papillomata, each composed of branching fibroelastic cores with a thin endocardial covering (Fig 2B).

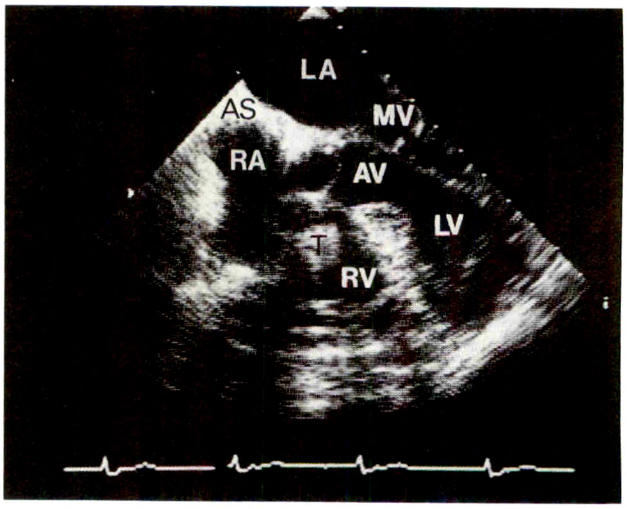

Fig 1. *Fibroelastoma of the septal leaflet of the tricuspid valve visualized on the ventricular side of the leaflet in late diastole.* (AS = *atrial septum;* AV = *aortic valve;* LA = *left atrium;* LV = *left ventricle;* MV = *mitral valve;* RA = *right atrium;* RV = *right ventricle;* T = *tumor.*)

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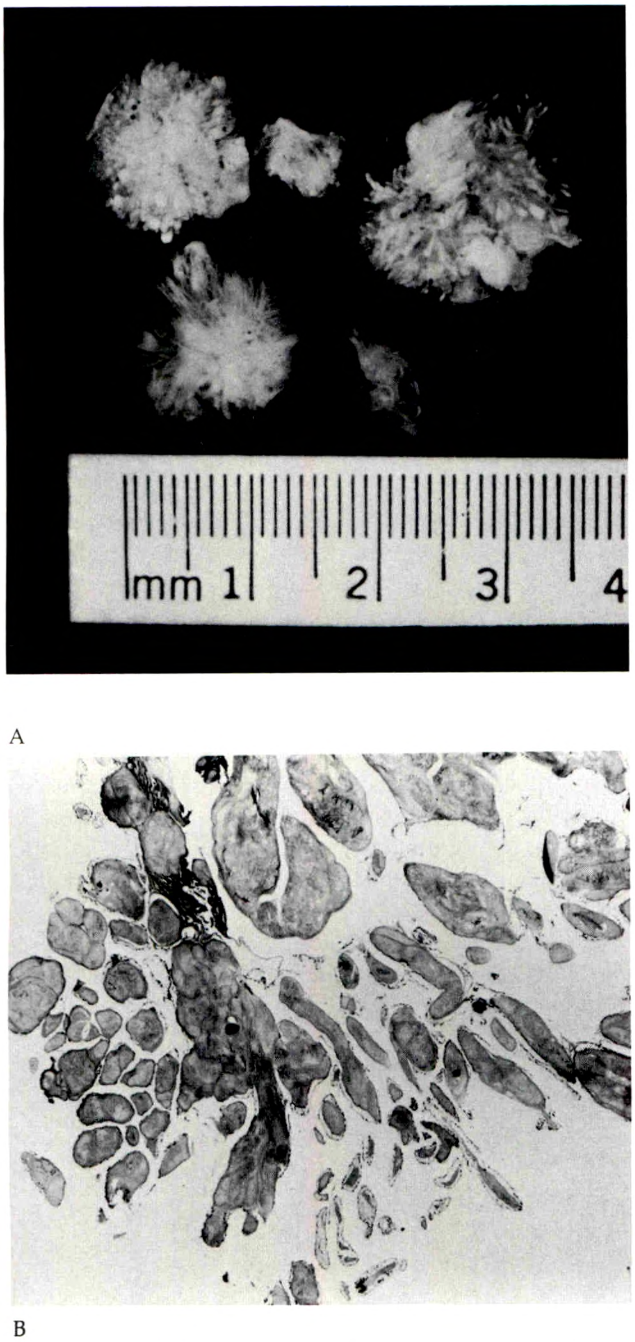

Fig 2. (A) Fine filiform projections of pom-pomlike masses of fibroelastoma. (Underwater gross photograph.) (B) Branching fibroelastic cores of connective tissue covered by a single layer of endocardial cells. (Verhoeff-van Gieson; ×100 before 37% reduction.)

The patient was hemodynamically stable postoperatively but with signs of recurrent right cerebral infarction (increased left-sided spastic hemiparesis and decreased mental status). Pneumonia due to *Pseudomonas aeruginosa* subsequently developed, and the patient died on postoperative day 15.

Postmortem examination showed marked right upper lobe pneumonia with abscess formation, a recent hemorrhagic infarct of the right occipital lobe of the brain associated with atheromatous embolism, and many other old infarcts. The heart weighed 406 g and showed left ventricular hypertrophy with severe coronary atherosclerosis. The saphenous vein graft from the aorta to the right coronary artery was patent. An additional 0.4-cm PFE was noted on one chorda to the septal leaflet of the tricuspid valve. No atrial or ventricular septal defects were noted. No masses or clots were found in the left side of the heart.

Comment

Papillary fibroelastoma has been described in patients 25 to 86 years of age [1], usually after 60 years of age. In one series [1], it constituted 9.5% of all primary tumors and cysts of the heart and pericardium in adults and represented 42 of 241 patients with benign tumors of the heart, making PFE the third most frequent benign tumor of the heart after myxoma (118 patients) and lipoma (45 patients). Among the 42 patients, 45 PFEs occurred equally in the left and right sides of the heart.

Since the advent of echocardiography, fewer than 20 PFEs have been detected in patients aged 20 to 75 years, with only 7 in patients aged 50 years or older [2, 6–10, current report]. Among patients studied echocardiographically, some had symptoms that could be attributed to tumor emboli to the brain [4, 6, 7] or had cardiac-related symptoms [2, 3, 5, 9, 10]; one has had no symptoms [10]. All echocardiographically studied lesions occurred in the left side of the heart, except for three on the tricuspid valve [2, 3, current report]. It may be that left-sided lesions are more likely to be symptomatic and therefore are detected by echocardiography at an earlier age.

Transesophageal echocardiography is an excellent technique for studying intracardiac masses because the images obtained usually are far superior to those from the transthoracic approach. The transesophageal approach also allows intracardiac shunts to be detected, if present, so that cardiac catheterization studies usually can be limited to coronary angiography alone in patients likely to have coronary artery disease. Additionally, intraoperative transesophageal echocardiography can be a useful adjunct for precise localization of intracardiac tumors for surgical excision and for assessing the adequacy of septal and valve repairs when necessary.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1993 may begin the recertification process in 1991. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1991. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Surgical Repair of Wolff-Parkinson-White Syndrome Complicated With Myocardial Bridging

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Myocardial bridging causes myocardial ischemia during supraventricular tachycardia. We present a case of Wolff-Parkinson-White syndrome combined with myocardial bridging. The patient complained of angina pectoris during paroxysmal supraventricular tachycardia because of severe constriction of the left anterior descending coronary artery during systole. A myocardial scintigram revealed myocardial ischemia in the anteroseptal wall during paroxysmal supraventricular tachycardia. Myotomy to prevent myocardial bridging and interruption of the accessory conduction pathway was successfully accomplished in a one-stage operation.

(Ann Thorac Surg 1991;51:119–21)

The development of electrophysiological studies of arrhythmia has motivated an increase in the number of operations for Wolff-Parkinson-White (WPW) syndrome, and it has been indispensable for the success of this operation. After the first surgical cure reported by Cobb and colleagues [1], a long series of operations for WPW syndrome was reported by a group from Kanazawa University [2] and other groups. According to these reports, the frequency of concurrent cardiac diseases that require surgical treatment in patients with the WPW syndrome is about 20% [2,3].

Myocardial bridging is an anomaly of the coronary artery, showing stenosis of the coronary artery during systolic phase. Tachycardia such as paroxysmal supraventricular tachycardia (PSVT) reduces coronary blood flow during diastole and causes myocardial ischemia in patients with severe myocardial bridging [4].

In this report, we present a case of WPW syndrome associated with myocardial bridging in a patient who complained of palpitation and angina pectoris during PSVT because of myocardial bridging.

The patient, a 31-year-old man, was admitted to Hiroshima University Hospital for progressively increasing tachycardia with angina pectoris that originated 15 years earlier. Electrocardiograms showed short PQ interval and wide QRS wave with delta wave, and we diagnosed his condition as WPW syndrome (type A). Electrophysiological study revealed that an accessory conduction pathway existed in the posterolateral region of the left atrium. A coronary arteriogram during PSVT showed 90% stenosis of the left anterior descending artery during systole (Fig 1) and suggested myocardial bridging. A myocardial scintigram (thallium 201) during PSVT showed myocardial ischemia in the anteroseptal wall of the left ventricle (Fig 2). Because PSVT accompanied by anginal attack occurred readily, we elected to proceed with operation.

Intraoperativemapping revealed an accessory conduction pathway located in the posterolateral wall of the left atrium. The patient was cooled to 28°C after initiation of cardiopulmonary bypass. While the heart was fibrillating by cooling, supraarterial myotomy for myocardial bridging was performed upon the muscle of the left anterior descending coronary artery through the length of 2 cm. After aortic cross-clamping, the heart was arrested with cold cardioplegic solution and the left atriotomy was made. A 3-cm endocardial incision around the posterior valvar annulus, extending from the anterolateral commissure to the center of the posterior mitral leaflet, was then made. The incision was made inferiorly so that the left ventricle was exposed, and cryoablation (−60°C, 2 minutes) was carefully applied to the both edges of the adipose tissue on the annulus. Postoperative epicardial mapping revealed that the accessory conduction pathway was completely interrupted.

The postoperative course was uneventful. The coronary angiogram showed that myocardial bridging disappeared and coronary squeezing did not arise during systole under high-frequency stimulation by atrial pacing (Fig 3). The patient continues to be asymptomatic at 4 months of follow-up without any drug.

Comment

In 1968, Cobb and colleagues [1] successfully treated a patient with type B WPW syndrome by epicardial ventric-

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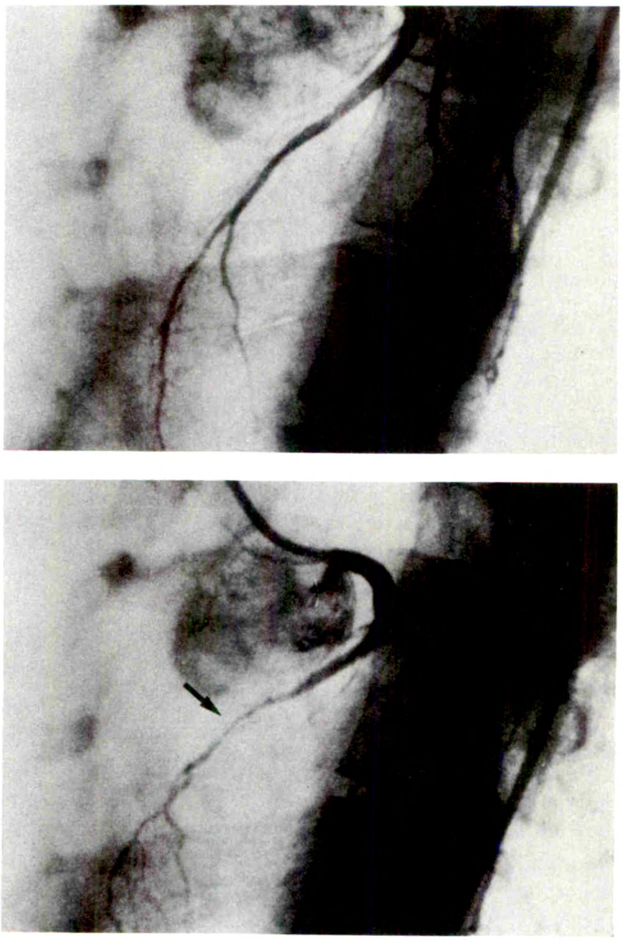
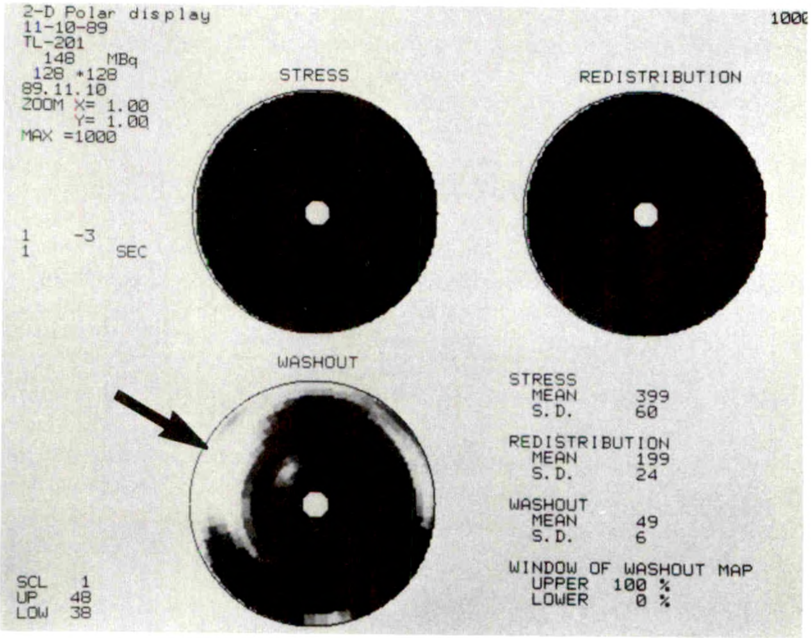


Fig 1. Preoperative coronary angiogram (hepatoclavicular position, 60 degrees). Coronary cineangiography revealed 90% stenosis of the left anterior descending coronary artery in systole during paroxysmal supraventricular tachycardia (arrow) *and dilatation of the same artery up to the normal caliber in diastole.*

ular interruption. Owing to the advancement of electrophysiological studies, the number of operations for WPW syndrome has increased. According to the reports by Iwa [2], Campbell [3], and their associates, the frequency of cardiac disorders concurrent with WPW syndrome is about 20% to 30%. Iwa and associates [2] reported 29 cases of concurrent cardiac diseases treated at the time of operation for 160 cases of WPW syndrome: 21 cases were congenital cardiac diseases, including 17 cases of Ebstein's anomalies and 4 other congenital diseases. Another 8 cases were acquired cardiac diseases consisting of 7 valvar diseases and coronary disease. Four of the 29 patients died postoperatively, and mortality for operation on patients with concurrent cardiac diseases (13.7%) was higher than that without them (0%). Wolff-Parkinson-White syndrome and Ebstein's anomaly are frequently associated with respect to their etiology and pathological features and should be treated surgically at the same time [5]. Other associated cardiac diseases are considered to be unrelated to WPW syndrome.

Myocardial bridging produces constriction of the coronary artery during systole. The degree of narrowing of the left anterior descending artery during systole was graded 3 (greater than 75%), 2 (50% to 75%), or 1 (less than 50%) [4]. Nobel and colleagues [4] reported that patients with grade 3 narrowing showed myocardial ischemia in the anterior wall and complained of angina during pacing at 150 beats/min. Under the condition of tachycardia greater than 120 beats/min, coronary blood flow during diastole decreases to 50%, and the systolic flow ratio increases comparatively. In a case of severe myocardial bridging, tachycardia is associated with a decreased systolic flow/total flow ratio, increased duration of systole, a lag in diastolic flow, and functional deterioration [6]. Functional abnormalities resulting from the flow discrepancies at heart rates of more than 150 beats per minute owing to

Fig 2. Myocardial scintigram of the left ventricle (thallium 201). The myocardial scintigram (washout ratio) showed myocardial ischemia of the anterolateral wall of the left ventricle (arrow), *which was detected by the difference in thallium distribution during stress (paroxysmal supraventricular tachycardia) and rest.*



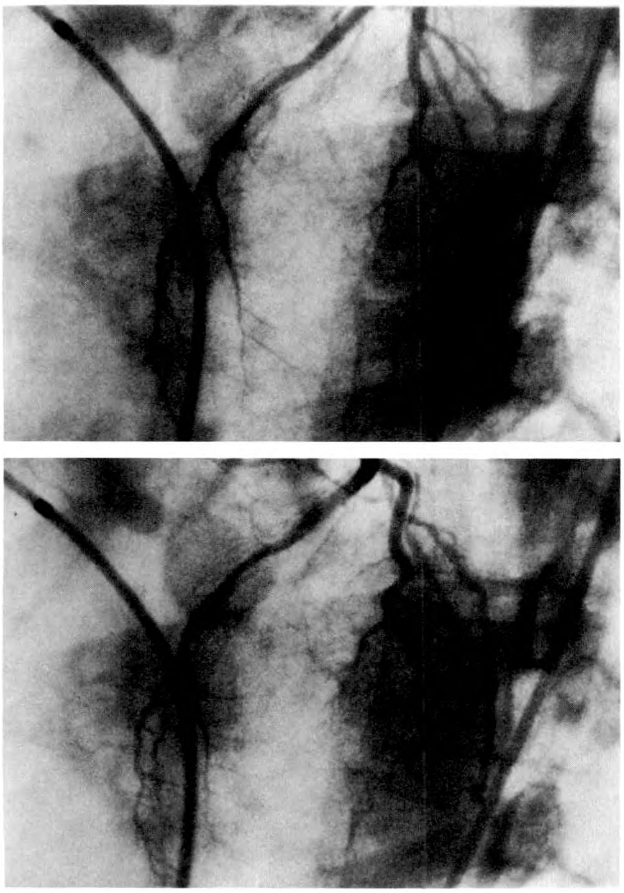


Fig 3. Postoperative coronary angiogram (hepatoclavicular position, 60 degrees). Myocardial bridging over segment 7 of the left anterior descending coronary artery was interrupted, and the artery was not stenotic during systole and diastole under high-frequency atrial pacing.

WPW syndrome may have accounted for our patient's symptoms.

Faruqui and colleagues [7] reported a case of supraventricular tachycardia, due to WPW syndrome, and severe chest pain caused by myocardial bridging; they lysed the bridge partially after saphenous vein grafting to the left anterior descending artery. They also treated the supraventricular tachycardia with propranolol, instead of surgical interruption of the accessory conduction pathway.

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Arterial Switch Procedure in an Adult

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The arterial switch procedure has been shown to offer both anatomic and physiologic correction in infants and children with transposition of the great arteries and ventricular septal defect. We believe that adults may also benefit in some circumstances, as evidenced by the case of a 22-year-old man who underwent successful operation after having initially undergone pulmonary artery banding for transposition with ventricular septal defect in 1967 when he was 5 months of age.

(Ann Thorac Surg 1991;51:122–4)

Before the arterial switch procedure was introduced, surgeons had limited options for treating patients with transposition of the great arteries and a nonrestrictive ventricular septal defect (VSD). Usually, they performed staged operations, in which palliative pulmonary artery banding was done to protect the pulmonary vasculature, followed later by a more definitive repair when the circumstances were appropriate. The second-stage operation usually included atrial switching techniques, such as those of Mustard and Senning, with or without VSD closure. Other patients received conduits in the manner of Rastelli. Unfortunately, these operations have yielded disappointing results in patients with a VSD [1].

Because of anatomic and physiologic advantages, pulmonary artery banding followed by the arterial switch procedure and VSD closure may afford better results in patients without irreversible pulmonary disease. Moreover, in select patients, older age may not be a contraindication, as evidenced by our experience with a 22-year-old man who had undergone pulmonary artery banding in infancy.

An infant with transposition of the great arteries and VSD underwent palliative balloon atrial septostomy at the Texas Children's Hospital shortly after his birth in 1967. At 5 months, increasing cyanosis and pulmonary artery hypertension necessitated operation. A Blalock-Hanlon septectomy and pulmonary artery banding were done to relieve the symptoms. When the patient was 5 years old, catheterization at another institution revealed suprasystemic pulmonary artery pressures: pulmonary artery pressure was 108/37 mm Hg (mean, 60 mm Hg) and aortic pressure was 105/68 mm Hg (mean, 80 mm Hg). His condition was considered inoperable because of the likelihood of irreversible pulmonary vascular changes. He was subsequently lost to follow-up.

Catheterizaton studies done at another hospital when the patient was 19 years old revealed that his right pulmonary artery pressure was considerably lower (36/20 mm Hg; mean, 28 mm Hg). In addition, angiographic studies, which allowed visualization of the transposition and the nonrestrictive VSD, showed normal ventricular function. The left coronary artery was not seen, but the right appeared normal. The hematocrit at that time was 0.59, with an oxygen saturation of 0.80.

The patient returned to the Texas Heart Institute for further studies when he was 22 years old. Catheterization revealed a slightly elevated right pulmonary artery pressure (38/22 mm Hg; mean, 32 mm Hg); pulmonary vascular resistance was 5.1 Wood units, and the left-to-right shunt ratio was 1.1:1. The angiogram (Fig 1) revealed the pulmonary artery band in place and normal peripheral pulmonary vessels. The coronary anatomy was normal, and pulmonary wedge angiograms revealed normal pulmonary vasculature. Arterial switch repair with VSD closure was recommended.

The operation was performed under hypothermic (25°C) low-flow cardiopulmonary bypass with aortic and bicaval cannulation. Cold (4°C) crystalloid cardioplegia (10 mL/kg) was infused through the aortic root after aortic cross-clamping. The ligamentum arteriosum was divided and oversewn. The pulmonary artery and its branches were mobilized to the hila, and the aorta was transected above the aortic valve commissures. The pulmonary artery band was removed, and the narrowed segment was excised. The coronary ostia were excised with surrounding U-shaped flaps of aortic wall. The coronary arteries were then mobilized to the extent that they could be sewn, tension-free, to vertical incisions in the anteriorly facing pulmonary sinuses. The Lecompte [2] maneuver was then performed, and the proximal pulmonary artery was anastomosed to the distal aorta with a continuous 5-0 polypropylene suture. The gaps in the aortic sinuses were then repaired with autologous glutaraldehyde-tanned pericardial patches, after which the proximal aorta was anastomosed to the distal pulmonary artery. The right atrium was opened and the VSD repaired through the tricuspid valve with a double-velour knitted Dacron patch and a continuous 5-0 polypropylene suture. The atrial septal defect was repaired similarly.

The patient required vasopressor support (dobutamine, 5 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}) at the termination of cardiopulmonary bypass. In the early postoperative period, mild coagulopathy was noted but resolved with blood compo-

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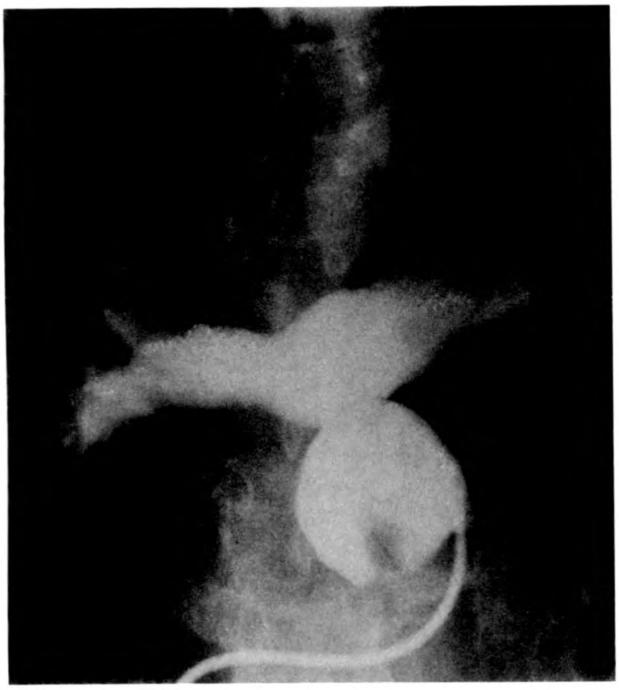

Fig 1. Pulmonary artery band with normal peripheral pulmonary vessels.

nent therapy. Initial extubation was accomplished on postoperative day 3, but the patient experienced pulmonary edema and required reintubation and vasopressor support (dobutamine, 15 mg · kg^{-1} · min^{-1}). Echocardiographic studies revealed poor left ventricular function at that time, but the patient was reextubated on postoperative day 4 and weaned from vasopressor support during the next 3 days. Since then, his recovery has been uneventful. At follow-up 7 months later, he had returned to normal activities and was working full time. Color-flow Doppler and echocardiographic studies demonstrated a trace of aortic and tricuspid regurgitation with a normal shortening fraction. The cardiothoracic ratio on chest roentgenogram had substantially decreased to 0.55.

Comment

The arterial switch procedure has gained acceptance in the treatment of neonates with transposition of the great arteries and VSD [3]. The operative mortality associated with this operation has decreased with improvements in neonatal perfusion techniques and increasing operative experience [4]. The timing of the operation, however, has been of concern, given that the left ventricle rapidly regresses in the presence of low pulmonary artery pressure. Although preliminary pulmonary artery banding [5] has been used to maintain the integrity of the left ventricle in infants with an intact septum, it carries an intrinsic risk of morbidity and mortality, which probably outweighs the risk of primary repair in the neonatal period [3, 6]. Despite the risk, pulmonary artery banding followed by arterial switching at a later date has advantages over atrial switching or the Rastelli-type repair in patients with transposition and VSD who for various reasons may not be considered candidates for arterial switch with VSD closure in the neonatal period.

Atrial switching techniques are associated with long-term sequelae, such as atrial arrhythmias, progressive right ventricular failure, tricuspid insufficiency, and vena caval obstruction, which result in long-term morbidity and a high late mortality [3, 7]. Some of these problems are related to the fact that the right ventricle is not suited to maintain systemic circulation over the long term.

Similarly, Rastelli-type conduit repairs have several disadvantages. Specifically, it may be technically difficult to direct left ventricular outflow to the aorta without enlarging the VSD or creating residual left ventricular outflow obstruction. In addition, conduit reconstruction of the right ventricular outflow tract leaves the patient with all the disadvantages of a conduit, including susceptibility to infection and the development of neointimal hypertension with conduit obstruction and valve deterioration.

In contrast, if pulmonary artery banding has prevented left ventricular regression and irreversible pulmonary vascular disease, the arterial switch procedure, which allows the left ventricle to maintain systemic circulation, is both anatomically and physiologically sound. Furthermore, older age does not appear to be a limiting factor. Our patient was 22 years old at the time of the arterial switch operation and has fared well. Technically, the procedure was quite easily accomplished, with no problems related to coronary transfer, pulmonary artery debanding, or reconstruction of the pulmonary artery and aorta. We believe that the catheterization data obtained when the patient was 5 years old were inaccurate. The measurement of spuriously low distal pulmonary artery pressures was probably caused by placement of the proximal holes of the multihole catheter near the pulmonary artery band. The patient's pulmonary vasculature had been well protected from the time of banding. Thus, we were provided a unique opportunity to observe the long-term effects of pulmonary artery banding on valve and ventricular function, both of which were well preserved at the time the patient finally returned for follow-up. Initial short-term postoperative follow-up also indicates that the effects of long-term cyanosis were mostly reversible as the patient's nail clubbing has resolved and left ventricular function appears to be normal.

The ultimate success of the arterial switch procedure will be determined by long-term follow-up with specific attention paid to potential long-term complications, such as pulmonary, aortic, or coronary artery stenosis and aortic or pulmonary valve regurgitation. The encouraging results to date, however, seem to indicate that those patients who have undergone pulmonary artery banding for transposition of the great arteries with VSD will be best served by debanding, VSD closure, and switching of the great vessels as their definitive operation. The case reported herein illustrates that this can be accomplished even many years after initial palliation.

Ascites After Rupture of Dissecting Aortic Aneurysm Into the Right Atrium

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We report successful repair of an aneurysmal aorta–right atrial fistula causing intractable ascites. The clamped "ascending aorta" was drained for mixed return after perfusion through the femoral vessels and opened during hypothermic arrest. Return cannulation through the fistula permitted definitive repair.

(Ann Thorac Surg 1991;51:125–7)

Formation of an aorta–right atrial fistula is a rare complication of aortic dissection [1]. Rupture into the right heart is often fatal [2, 3], but a few cases of successful surgical repair have been reported [1, 2, 4]. The clinical findings in these patients were relatively uniform, comprising dissection and right ventricular overload. We describe a case in which intractable ascites developed.

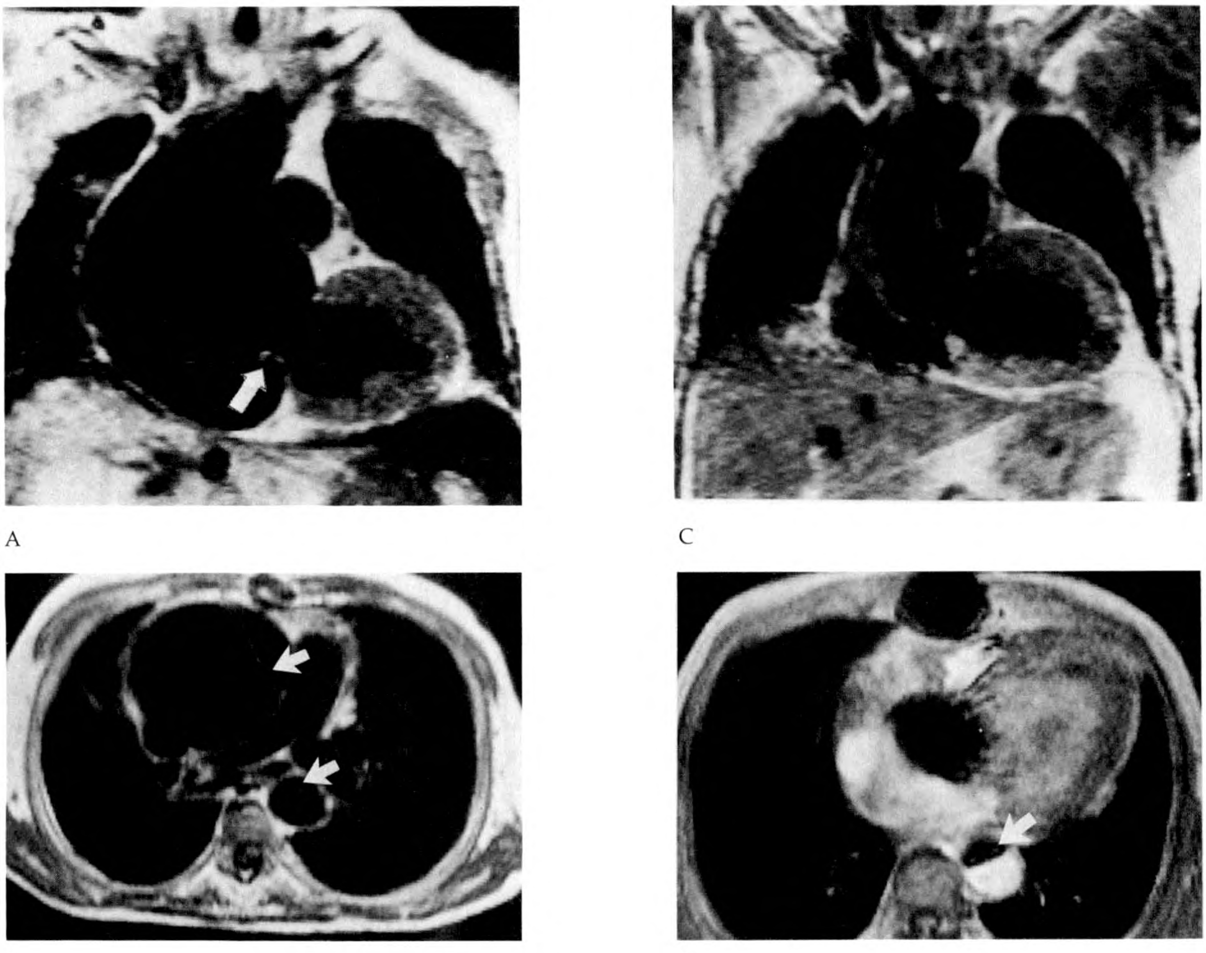

Fig 1. Magnetic resonance imaging before operation (A, B) and at 1-year follow-up (C, D). Arrows *indicate dissection near the aortic annulus, extending into the descending aorta, ie, de Bakey type I.*

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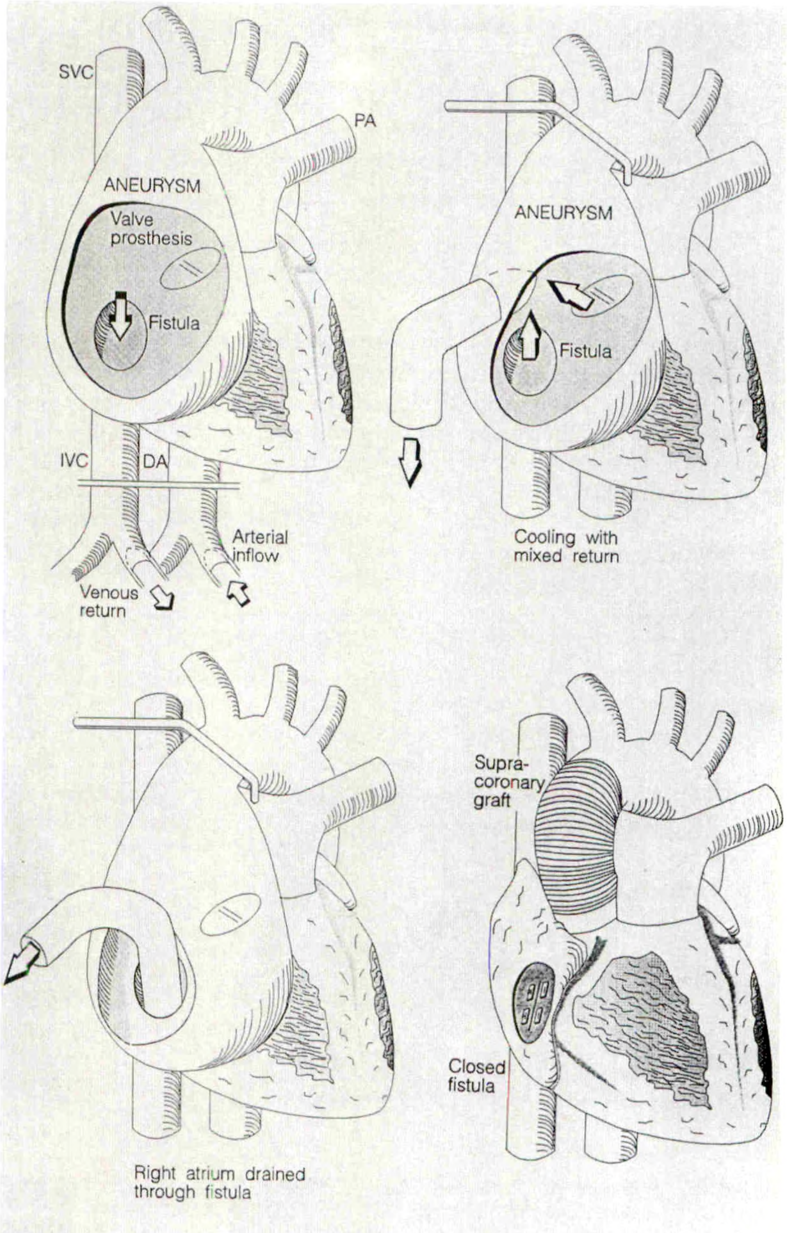
Fig 2. Steps of the repair. (DA = *descending coronary artery;* IVC = *inferior vena cava;* PA = *pulmonary artery;* SVC = *superior vena cava.)*



The patient underwent an uncomplicated aortic valve replacement at age 45 years owing to severe aortic insufficiency. The ascending aorta, however, was found to be dilated, with thinning of its wall. Three months later he suffered a de Bakey type I aortic dissection (Fig 1). Operation was not considered at that stage because the aortic prosthetic valve was competent, an unwise decision as after 3 years the patient had intractable ascites. A prominent systodiastolic cardiac murmur, magnetic resonance imaging, angiography, and cardiac catheterization confirmed the presence of an aorta–right atrial fistula with 75% shunt.

Repair was begun with perfusion through the femoral artery and vein. At sternotomy the right atrium was beyond reach and therefore the aorta was clamped proximal to the truncus, after which the aneurysm was cannulated for return and mixed right to left bypass to full flow. At 20°C central temperature the aneurysm was opened during circulatory arrest, the return cannula was guided through the fistula to the right atrium, and full flow was reestablished. Despite gross pathology of the ascending aorta, the prosthetic valve site and coronary orifices were without major disease and an intimal rupture at the aortotomy suture line was the probable source of the dissection and fistulation. The aneurysm was replaced with a tubular graft and the fistula was closed at decannulation (Fig 2). Weaning from cardiopulmonary bypass was uneventful with normalized pulmonary artery pressure, from 70 mm Hg systolic.

The postoperative course was benign without recurrence of ascites and the anatomical result of the repair remains good at 1 year follow-up (Figs 1, 3). Histologic examination of an aortic wall specimen revealed idiopathic medial necrosis.

Comment

Rupture of an aneurysm of the ascending aorta into the right atrium is a rare event. Reports on this condition have described a relatively uniform symptomatology, comprising

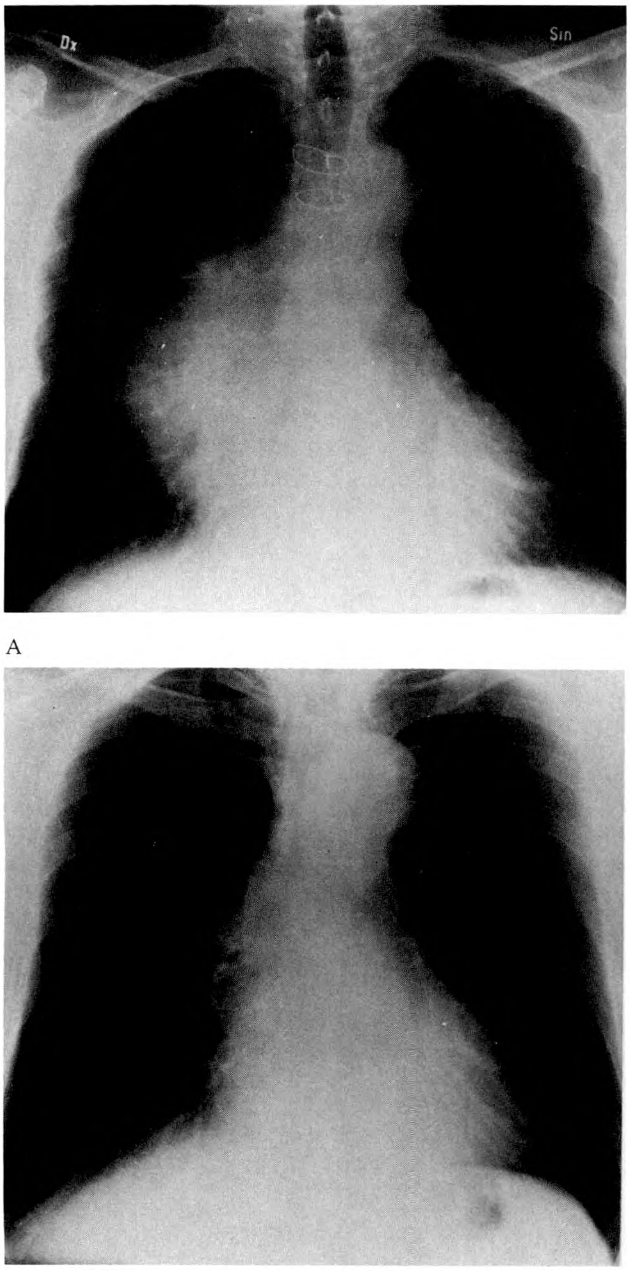


Fig 3. Chest roentgenogram before (A) and 1 year after operation (B).

chest pain and, in some cases, dyspnea [1–10]. Signs of increased right ventricular volume work, such as distention of the jugular veins, are also common, as is a systodiastolic murmur. A delay of several months between onset of symptoms and diagnosis is common. Mortality is high: 5 of the 12 reported patients. Two of these five deaths occurred before diagnosis, one after heart catheterization, and two postoperatively. Six patients, including ours, survived after surgical correction, with reported follow-up of 6, 6, 8, 9, 12, and 24 months. The fate of 1 patient was not reported. The possible mechanism for development of aorta–right atrial fistula is dissection into the aortoatrial space near a commissure of the aortic annulus, at which site the aortic media is not continuous with the annulus. From here the dissection enters the atrium. Diagnosis in previously reported cases was established from physical signs, cardiac catheterization, aortography [10], and echocardiography [1, 5, 11]. In our case magnetic resonance imaging was useful in establishing the diagnosis.

Our patient differs from other reported cases in the development of intractable ascites without recurrence after operation. We are aware that the entire complication could have been prevented by early surgical treatment of the dissection or, better, by insertion of a composite graft at the time of aortic valve replacement.

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New Surgical Approach to Complicated Gastroesophageal Reflux Disease: Transthoracic Parietal Cell Vagotomy

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Surgical treatment of peptic stricture of the esophagus associated with columnar (Barrett) metaplasia can be a difficult problem. Collis-Nissen fundoplication restores an intraabdominal antireflux barrier for most cases of peptic stricture; however, 20% of patients may have persistence of pathological acid reflux. By reducing acidity of postoperative reflux, parietal cell vagotomy may complement nonresectional surgical results for Barrett stricture.

(Ann Thorac Surg 1991;51:128–30)

This report describes the combination of transthoracic parietal cell vagotomy and Collis-Nissen fundoplication to manage a case of peptic stricture associated with Barrett metaplasia. The use of Collis-Nissen fundoplication can improve surgical results in the treatment of reflux-induced esophageal stricture [1]. Pathological 24-hour acid reflux may be seen in up to 20% of patients after this procedure [2]. This continued acid reflux exposure may be an important factor leading to recurrent peptic stricture and dysplasia in the specialized esophageal epithelium. The addition of transthoracic parietal cell vagotomy to Collis-Nissen fundoplication provides a new balanced approach for advanced gastroesophageal reflux disease that may improve the results with nonresectional surgical treatment.

A 48-year-old man with several years of heartburn and regurgitation treated with cimetidine and antacids was admitted to the medical service complaining of progressive dysphagia and a 15.8-kg weight loss over a 2-month period. An upper gastrointestinal barium study showed a mid-esophageal stricture with subtotal obstruction (Fig 1). Esophagoscopy showed a tight stricture at 28 cm from the incisors with associated erosive esophagitis. Biopsy of the esophagus in the area of the stricture documented specialized columnar (Barrett) epithelium without dysplasia. The stricture was sequentially dilated in four treatment sessions from a 12F to a 48F circumference. A repeat endoscopic examination after 6 weeks of medical antireflux therapy (which included H_2 blockers) showed a 6-cm hiatal hernia with the gastroesophageal junction at 35 cm from the incisors. Columnar epithelium lined the distal esophagus to the stricture area at 28 cm. The esophagitis was mildly improved but some erosive changes persisted. In view of the patient's longstanding history of reflux symptoms, Barrett esophagus, and associated stricture, surgical therapy was believed to be warranted. Preoperative manometry demonstrated lower esophageal sphincter hypotension (mean pressure < 5 mm Hg) and normal esophageal peristalsis. Gastric secretory studies showed a basal acid output of 4 mmol/h and a pentagastrin-stimulated maximal acid output of 10 mmol/h.

A seventh interspace thoracotomy was performed and intraoperative esophageal dilation to 54F was accomplished. Serious periesophagitis was noted. The vagal trunks were identified and the hernia sac was opened. The proximal two short gastric vessels were ligated to adequately mobilize the gastric fundus for plication. Parietal cell vagotomy was then carefully performed through the esophageal hiatus from the distal 5 cm of the esophagus to beyond the proximal nerves of Latarjet along the lesser gastric curvature (Fig 2). A 4-cm gastroplasty was then fashioned around a 54F intraesophageal bougie. After mobilization of the esophagus, a 2-cm fundoplication was created around the gastroplasty tube (Fig 3). This repair was reduced through the esophageal hiatus without tension, and the diaphragmatic crura was approximated posteriorly. Figure 4 depicts the completed procedure as seen beneath the diaphragm. The patient's postoperative course was uneventful. A postoperative upper gastrointestinal series demonstrated an intact intraabdominal fundoplication without reflux, gastric stasis, or residual stricture (Fig 5). Gastric analysis was repeated 3 weeks after operation and showed a basal acid output of less than 0.1 mmol/h and a pentagastrin-stimulated maximal acid output of 0.2 mmol/h. Over a 9-month period of postoperative follow-up, the patient has done well without return of dysphagia or of gastroesophageal reflux symptoms.

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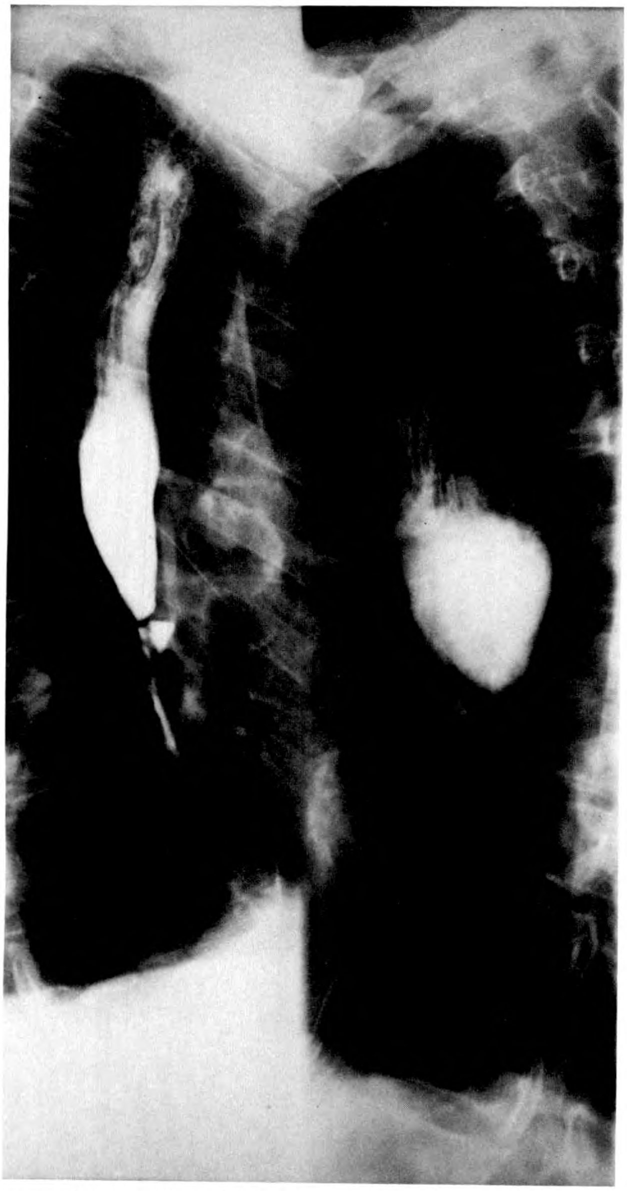

Fig 1. Oblique radiographs of high-grade mid-esophageal Barrett stricture with peptic ulceration.

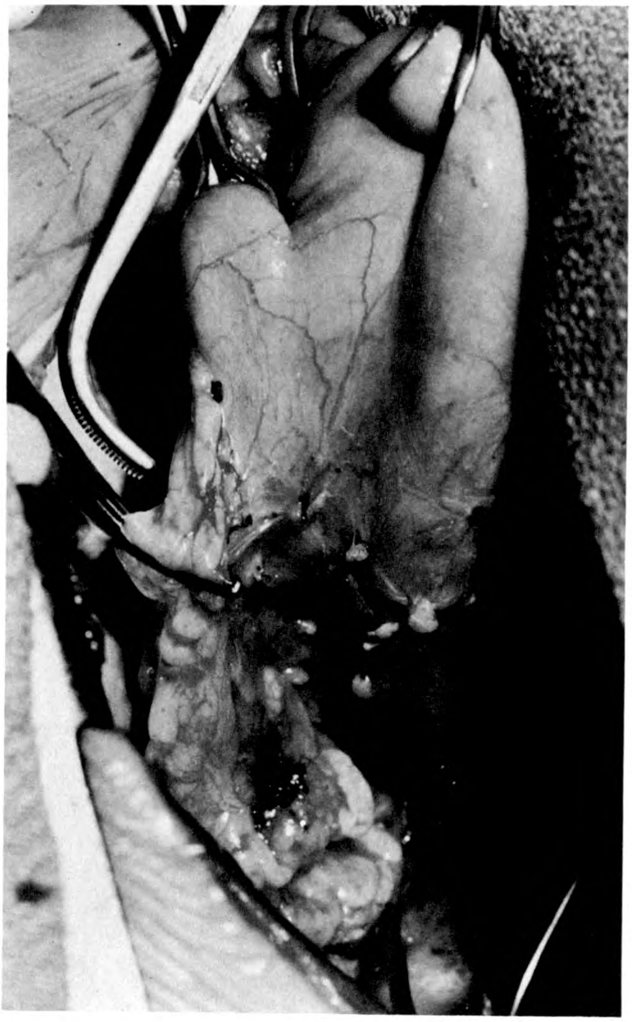

Fig 2. Parietal cell vagotomy progressing along the posterior lesser curvature as the stomach is advanced into the chest.

Comment

Lower esophageal sphincter hypotension and pathological acid reflux exposure is usually extreme among patients with Barrett metaplasia. This leads to a greater than 40% prevalence of epithelial ulceration with stricture and esophageal foreshortening with this reflux problem [3]. Medical management of this condition is centered around esophageal dilation and liberal use of gastric acid suppression with H_2 blockers and now omeprazole [4].

An operation for benign Barrett stricture should be considered for younger patients and for those individuals who require frequent dilations during medical therapy. Perioperative dilation of the stricture and an antireflux operation can usually control the process without the need for esophageal resection [5]. Nonetheless, standard antireflux procedures have been marginally successful in the treatment of reflux strictures [6].

The Collis gastroplasty allows restitution of an adequate intraabdominal segment of esophagus and reduction of the hiatal hernia without tension. Combining gastroplasty

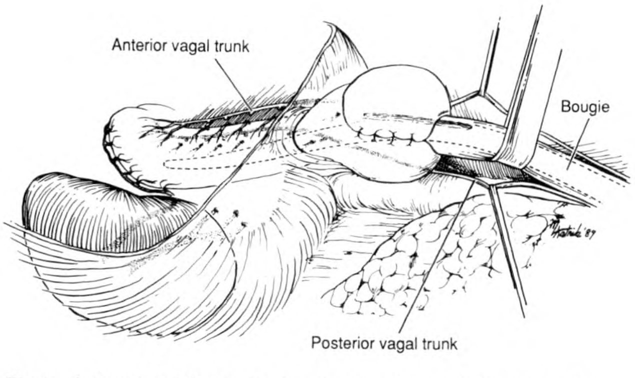

Fig 3. A 2-cm total fundoplication fashioned around the gastroplasty tube.

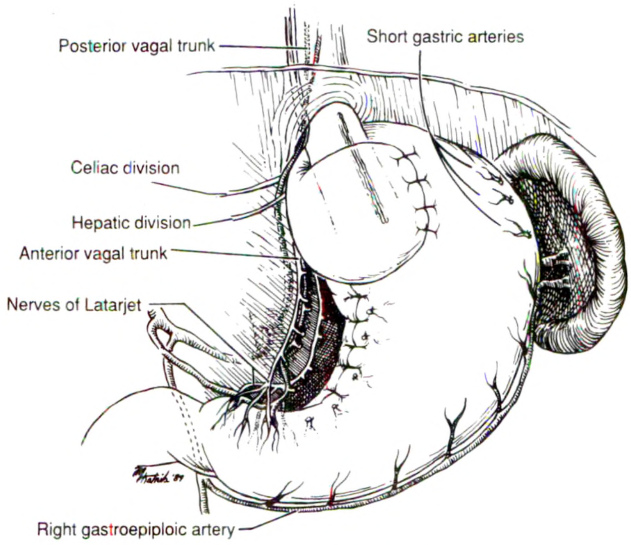

Fig 4. Abdominal view of the completed parietal cell vagotomy and Collis-Nissen fundoplication.

with total fundoplication has been reported to improve considerably the surgical treatment of reflux-induced strictures [1]. Stirling and Orringer [2] have reported a 90% success in treating esophageal stricture with the transthoracic Collis-Nissen procedure although 20% of their patients studied postoperatively were found to have abnormal 24-hour acid reflux testing. This continued acid reflux exposure may contribute to recurrent stricturing and further occult esophageal epithelial damage.

Truncal vagotomy with drainage and gastric resection have been combined with hiatal hernia repair in the past, but postoperative side effects have outweighed the benefit from the gastric acid reduction achieved [7]. Others [8] have endorsed adjunctive parietal cell vagotomy with transabdominal antireflux operation because of its acid-lowering potential and its low occurrence of postvagotomy dumping, diarrhea, or gastric atony. Transthoracic parietal cell vagotomy can be safely accomplished through the hiatus with minimal difficulty. Patients with documented gastric hyperacidity and extensive reflux injury to the esophagus may be particularly suited for this new balanced transthoracic antireflux procedure.

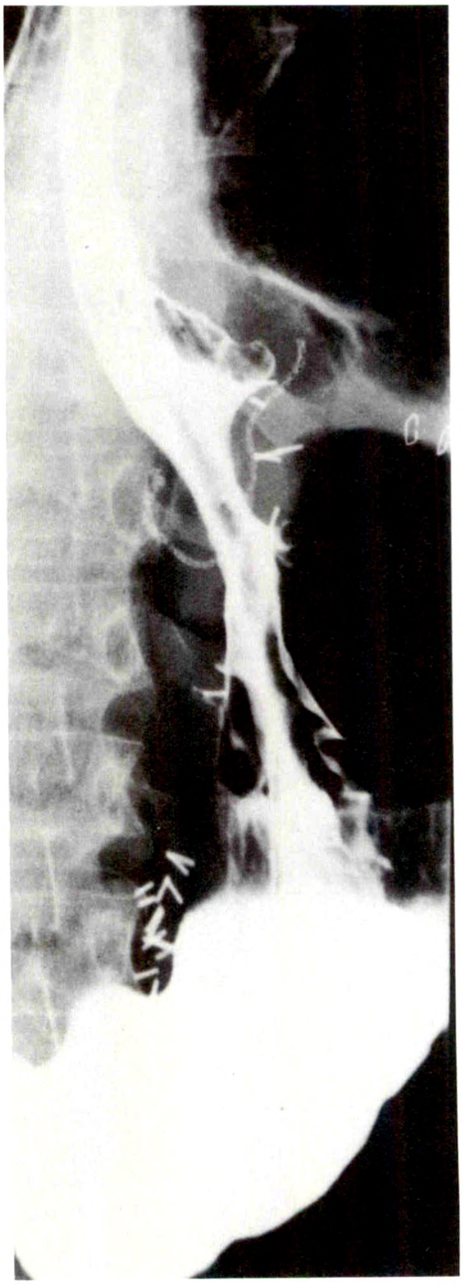

Fig 5. Postoperative upper gastrointestinal study demonstrating the staple line of the fundic wrap and vascular clips at the distal extent of the parietal cell vagotomy.

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Left Ventricular Aneurysm Secondary to Behçet's Disease

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A 16-year-old boy with Behçet's disease who was seen with thrombophlebitis of the leg was found to have coronary artery occlusion with postinfarction left ventricular aneurysm. Recurrent femoral artery aneurysms and orogenital ulceration developed in him. The diagnostic features together with successful treatment of this patient and a discussion of Behçet's syndrome are presented.

(Ann Thorac Surg 1991;51:131–2)

Behçet's syndrome is a systemic disease of unknown origin in which the cardiovascular system is involved in 7% to 29% of cases, with recurrent superficial thrombophlebitis, aneurysms of the pulmonary and systemic arteries, pericarditis, myocarditis, endocardial fibrosis, conduction defects, and aortic regurgitation [1, 2]. We present a case of Behçet's disease with thrombophlebitis, thrombotic occlusion of the left anterior descending coronary artery with infarction and aneurysmal formation, and arteritis of the femoral artery with recurrent aneurysms.

A 16-year-old boy was admitted to the hospital with thrombophlebitis of the right leg. The laboratory test showed a fibrinolysis defect, and oral anticoagulant therapy was started. Routinely performed electrocardiography showed old anterior myocardial infarct: the history of the patient in fact showed a previous episode of severe chest pain with vomiting that was undervalued in the first instance. Cardiac catheterization showed proximal occlusion of the left anterior descending coronary artery and the left ventricular aneurysm. Three months after cardiac catheterization, pulsatile aneurysm developed at the puncture site of the femoral artery and was resected; the arterial wall was repaired with a saphenous vein patch. The aneurysm recurred again a month later, requiring a graft interposition to reconstruct the artery. At that time, Doppler echocardiography was performed, showing a new aneurysmatic ventricular pouch with a very thin wall in free communication with the left ventricular aneurysm previously noted (Fig 1). Surgical treatment was then advised. At operation, performed using cardiopulmonary bypass, a biloculated aneurysm was found in which the proximal part was probably the result of the anterior myocardial infarct whereas the distal one appeared to be of mycotic origin (Fig 2). The aneurysm was resected, and samples were sent for bacteriological and histological studies. The postoperative course was uneventful, but a month later, a pulsatile aneurysm recurred in the femoral artery, initially requiring iliac–femoral bypass and then, because of its recurrence in the distal anastomotic site, requiring reconstruction of the artery using a 7-mm Gore-Tex graft. The macroscopic appearance of the femoral aneurysm was of inflammatory origin, but all the cultures were sterile. During the patient's hospital stay, oral and genital ulcerations were noted and Behçet's disease was then suspected. The histological slides taken from the left ventricular and femoral artery aneurysms were then looked at again, and the diagnosis was confirmed by recognizing the typical appearance of Behçet's disease. Corticosteroid and immunosuppressive therapy was given; the boy recovered completely, and he is well after 16 months.

Comment

A syndrome characterized by the triad of recurrent orogenital ulcerations, relapsing iridocyclitis, and erythema nodosum was described by Behçet [3] in 1937. Since then many other clinical manifestations of the same disease were recognized, conferring the character of a systemic disease to Behçet's syndrome [4]. Its cause is unknown, but the pathogenesis is probably due to an immunopathologic disorder because of the characteristic vasculitis with early mononuclear and late polymorphonuclear cell infiltration that is always present in the involved organs and systems. This hypothesis is also supported by the good response to corticosteroid and immunosuppressive therapy [4].

The disease affect young adults especially in Japan, the Middle East, Cyprus, Turkey, and Greece with a prevalence of 10/100,000 population in Japan [4, 5]. Oral and genital ulcerations are nearly constant features. The eye may be involved resulting in inflammation of the anterior chamber, conjunctivitis, scleritis, retinal vasculitis, and optic neuritis [4]. Erythema nodosum, the third element of the syndrome, has been reported in about 80% of patients [6]. Inflammatory polyarthritis is present in about half of the patients and most often involves the superficial layers of the cartilages of the knees and ankles [4]. Neurological manifestations are related to meningoencephalitis, cranial nerve palsies, or pseudotumor cerebri,

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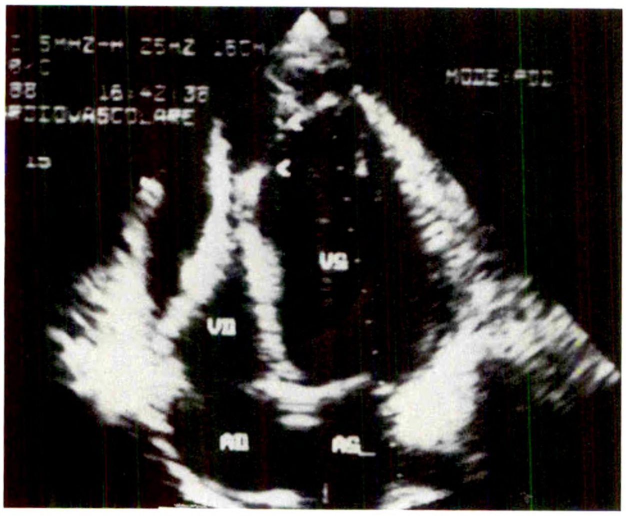

Fig 1. Preoperative two-dimensional echocardiogram demonstrating left ventricular aneurysm. Arrows *indicate the communication between the aneurysm and the left ventricle.* (AD = *right atrium;* AS = *left atrium;* VD = *right ventricle;* VS = *left ventricle.)*

but more often to brainstem involvement with dysfunction resembling minor strokes [4]. Decreased activity of the fibrinolytic system is responsible for thrombotic occlusion of the arteries and veins [6]. Cardiovascular involvement is present in 7% to 29% of the patients [1] and is characterized by recurrent thrombophlebitis; arterial occlusion; aneurysm of the aorta, its major branches, and peripheral arteries especially at the site of arterial punctures; aneurysm formation of the pulmonary artery; pericarditis; myocarditis; endocardial fibrosis; conduction defects; and aortic regurgitation [1, 6, 7–9]. In our patient, most of the cardiovascular manifestations of Behçet's syndrome were present; however, the macroscopic appearance of the myocardium involved in the ventricular aneurysm and of the aneurysm in the femoral artery were misleading in that they were strongly suggestive of infective process. The late appearance of orogenital ulceration led to the right diagnosis.

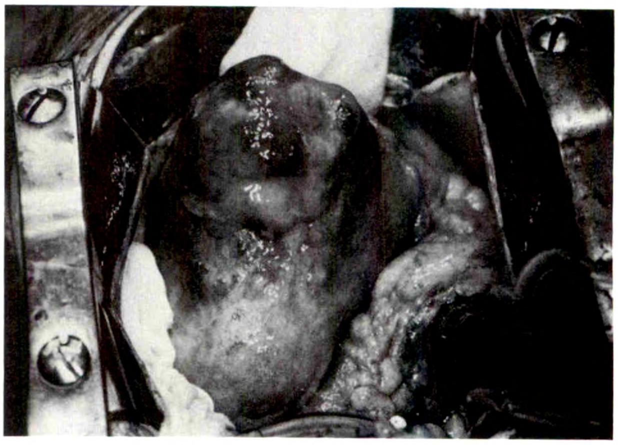

Fig 2. Intraoperative aspect of left ventricular aneurysm.

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Rectus Abdominis Muscle Flap With Microvascular Anastomoses for Repair of Recurrent Sarcoma

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After radical resection of a recurrent leiomyosarcoma, the thoracic wall was stabilized with a Gore-Tex graft. The skin and soft tissue defect was repaired with a large rectus abdominis flap in which the circulation was secured by end-to-end microvascular anastomosis of the inferior epigastric artery to the internal mammary artery, which had to be cut during tumor removal.

(Ann Thorac Surg 1991;51:133–5)

Radical resection and repair of large tumors penetrating through the wall of the thorax is always demanding, and musculocutaneous flaps are now generally used for this purpose [1]. As latissimus dorsi and pectoralis major flaps will not usually reach the lower part of the anterior thoracic wall, a transverse rectus abdominis musculocutaneous (TRAM) flap is most suitable in this area [2, 3]. This flap commonly involves complications, however, owing to the poor and variable circulation in the contralateral random portion of the flap [4]. It is also possible to transfer the TRAM flap to the thorax area as a free flap [5].

In the present case report, we describe the use of a large TRAM flap and a Gore-Tex graft (W.L. Gore & Co, Salzburg, Germany) for the correction of a large thoracic wall defect. The circulation in the flap was further improved by microvascular anastomosis of the inferior epigastric artery to the internal mammary artery and of the inferior epigastric veins to the cephalic vein.

Our patient was a 59-year-old man who had been operated on eight times for a recurrent soft tissue tumor on the right side of the thorax diagnosed as a leiomyosarcoma in 1980.

A new recurrence was noticed in October 1988. Preoperative computed tomography and ultrasonic examination showed a parasternal tumor infiltrating the thoracic wall in the region of the third and fourth ribs. It was poorly distinguishable from the surrounding tissues and measured 3 × 4 cm in diameter. No signs of metastases were observed.

A radical tumor excision was carried out. The area of skin removed measured 17 × 20 cm. The transthoracic excision was 10 × 10 cm and included the mid-portion of the sternum and the cartilages of the third and fourth ribs with the underlying pleura. The right internal mammary artery had to be sacrificed during the operation. The transthoracic defect was stabilized by suturing a 10 × 10-cm Gore-Tex (1 mm thick) graft to its margins, and reconstruction was achieved with a 17 × 20-cm musculocutaneous rectus abdominis flap that included both rectus muscles. The inferior epigastric vessels were severed and ligated bilaterally near their origin in the iliac vessels for inclusion in the flap. The flap was mobilized using the rectus muscles and was turned toward the area under repair. As the internal mammary artery supplying the right rectus muscle had been severed in connection with the radical excision of the tumor, the stump of the internal mammary artery was sutured end-to-end to the right epigastric artery. To ensure venous return, the inferior epigastric veins on both sides were sutured to the cephalic vein, which was turned from the right upper arm to the operative field. The anastomoses to the veins were made end to end and end to side. The abdominal wall was reconstructed below by suturing the lower portion of the rectus muscle to the arcuate line. To secure the posterior wall of the rectus muscle during the initial phase of healing, a Dexon net (Davis & Geck, Gosport Hampshire, England) was applied to the top of the muscle, and the skin was directly closed after subcutaneous mobilization (Figs 1–3).

Postoperative recovery was uneventful, and healing of the flap was excellent owing to the good circulation. The thorax drain was removed on the third postoperative day. A small skin portion at the margin of the abdominal closure was lost and was replaced with a free skin graft. The patient was discharged from the hospital on the 30th postoperative day. He was symptom-free at check-ups, and stabilization of the thorax was good. In terms of the histological reports, the operation was a radical one. No recurrences have been observed during a follow-up time of 1 year postoperatively (Fig 4).

Comment

The use of excisions of maximum extent together with a local plastic operation was not considered in this case because the patient had already been treated in this way eight times before and tumor residues had proved unavoidable. Instead, a more radical resection was now deemed necessary. A musculocutaneous latissimus dorsi reconstruction was not considered possible for this central defect, and thus a pedicled TRAM flap with additional microvascular anastomoses was preferred. The arterial

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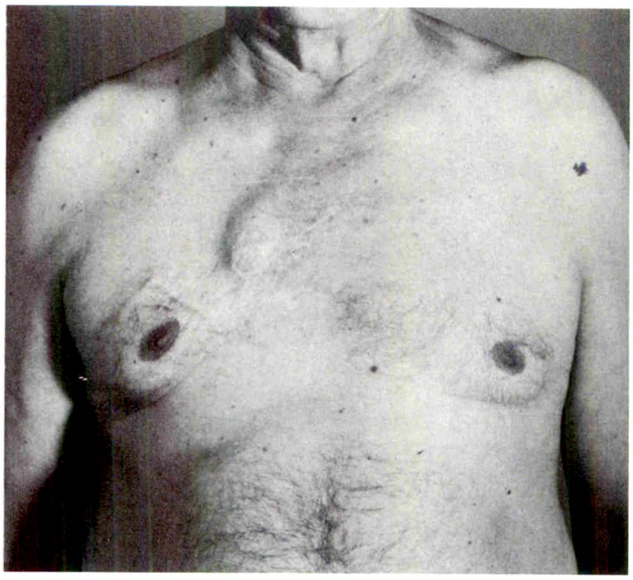

Fig 1. The recurrent tumor on the right side of the thoracic wall.

supply to this flap was through the left superior epigastric artery, the blood supply to the right epigastric artery being lost because it was necessary to sacrifice the right internal mammary artery during tumor removal. This was the reason for the additional microvascular anastomoses.

A conventional musculocutaneous TRAM flap is extensively used in reconstructions of the female breast after cancer operations, for instance [1, 3], but the contralateral random portion of the flap may occasionally be compromised and lead to skin or fat necrosis. Even a small, partial flap loss would be disastrous after a major, full-thickness thoracic wall excision. A microvascular TRAM flap also carries a high risk for complications [5], but the combination of a conventional TRAM flap with microvas-

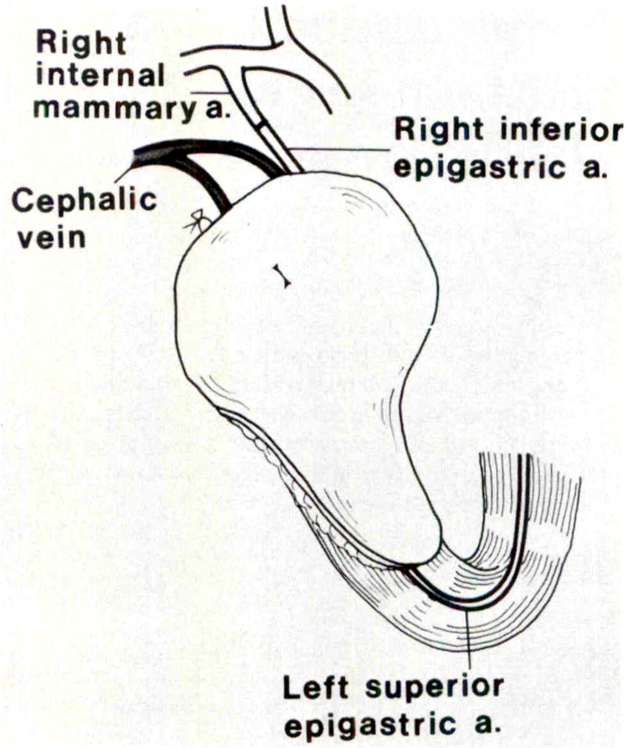
Right internal mammary a.
Right inferior epigastric a.
Cephalic vein
Left superior epigastric a.

Fig 3. Anatomy of the flap and location of the microvascular anastomoses. The rectus abdominis muscle flap used for reconstruction has an intact blood supply through the left superior epigastric artery. The blood flow to the flap was further secured by end-to-end anastomosis of the internal mammary artery to the right inferior epigastric artery. Venous return was ensured by end-to-end and end-to-side anastomoses of the inferior epigastric veins to the cephalic vein. (a = artery.)

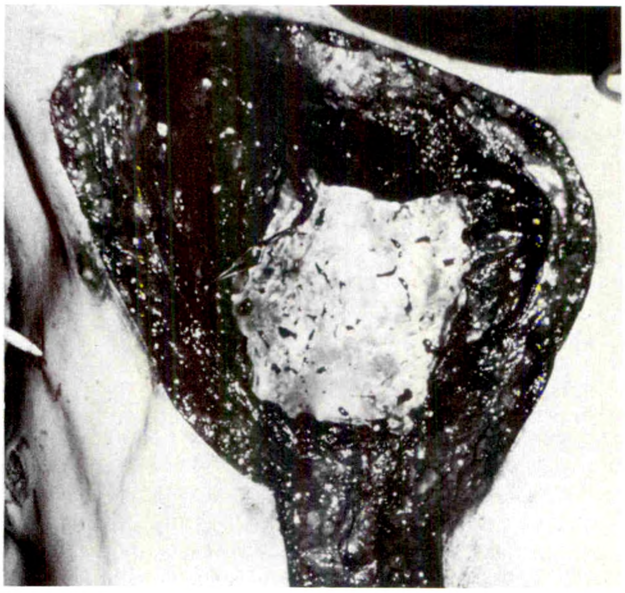

Fig 2. The excised area at the top, with the Gore-Tex graft in the middle of it. The internal mammary artery stump can be seen in clamps on the graft.

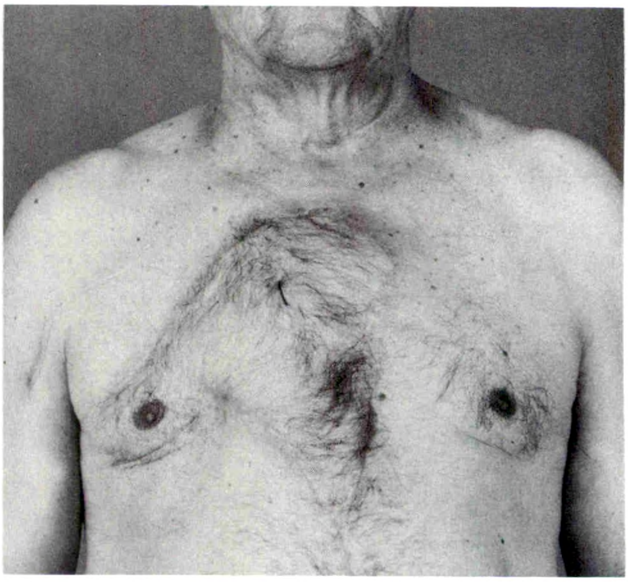

Fig 4. The result 1 year after the operation.

cular anastomoses has been found advantageous in reconstructions of the female breast [6].

In our case the combination of a conventional flap with microvascular anastomoses gives additional security to the reconstruction. This is especially important when treating a widespread tissue defect extending through the thorax. We believe that because the mammary artery supplying the flap had to be sacrificed in connection with resection of the tumor, the microvascular anastomoses securing the blood supply to the flap were extremely important for the good recovery of our patient.

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Continuous Retrograde Blood Cardioplegia

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We present a technique of myocardial protection using retrograde cold blood cardioplegia. This safe and simple method allows excellent continuous and homogeneous cooling of the heart during the ischemic period in all types of open heart operations.

(Ann Thorac Surg 1991;51:136–7)

Our cardioplegia delivery system involves the following: retrograde delivery of 100% oxygenated blood, use of a passive aortic root vent, and minimal use of crystalloid solutions. The cardioplegia pump is set up as seen in Figure 1. It contains a Shiley Buckberg delivery system (BCD Plus; Shiley, Inc, Irvine, CA) with a Digi-Dyne pressure monitor (Renal Systems, Minneapolis, MN). Cooling in the BCD Plus is accomplished by a sump pump placed in the bottom of our Sarns heater cooler. The cardioplegia circuit is primed with approximately 400 mL of Normasol solution (Abbott Laboratories, North Chicago, IL), and this is recirculated until bypass is initiated. A single two-stage cannula is generally used, with bicaval cannulation reserved for mitral and tricuspid valve procedures. A 15F DLP Gundry retrograde cannula (DLP, Inc, Grand Rapids, MI) is placed before bypass, and we have seen no hemodynamic consequence doing this. The cannula is molded to an 80-degree angle and placed through the atrium approximately 2.5 cm caudad to the atrial appendage and anteriorly. It is then manipulated *over the top* of the two-stage cannula; and without lifting the heart, it is directed posteriorly and to the left, where it easily slides into the coronary sinus as far as possible. Even in our early experience, this was possible in 95% of patients. Despite having the cannula almost to the left atrial appendage in the sinus, there is abundant venous collateralization, ensuring homogeneous cooling. The cannula is also less apt to pop out into the atrium. Right ventricular temperatures have been measured multiple times and have been consistently maintained at 13°C or lower after our initial dose.

The pressure line of the retrograde cannula is then zeroed so that the coronary sinus pressure can be easily measured by the perfusionist. High pressure limit is set at 50 mm Hg, and the system is programmed to automatically discontinue pumping if the pressure is exceeded. Simultaneous with the initiation of heart-lung bypass, the patient is exsanguinated to achieve a bypass hematocrit of 0.21. This is rapidly and easily done with a Cobe autologous blood management set. This amount of exsanguinated blood is calculated according to the formula in Table 1. The blood is kept for reinfusion after the bypass has been completed. Hemodilution eliminates the need for further crystalloid dilution of the blood cardioplegia as seen in the 4:1 delivery systems. When the bypass is begun, the patient is cooled to 25°C. We then use a 12-gauge passive vent in the ascending aorta. A 3/16-inch line is attached to the cannula and through gravity drains directly back into the venous reservoir, where it is returned to the extracorporeal circuit. This vent allows easy drainage of the continuous retrograde cardioplegia.

Oxygenated blood is now transferred from the top of the arterial filter to the cardiotomy reservoir (Fig 1). It is mixed with the Normasol prime so that a total of 800 mL is achieved. Sixteen millimoles of potassium is added directly to this volume as it is recirculated. After the cross-clamp is applied, a 3-mL syringe is used to fill the retrograde cannula balloon. The cardioplegia is given at 300 mL/min, maintaining a coronary sinus pressure of less than 50 mm Hg for the next 3 to 5 minutes. The temperature of the solution is 4°C. Clinically, the cardioplegia can be seen to be working well by palpating rapid cooling of the left ventricle and also by seeing distention of the middle cardiac vein next to the posterior descending artery. After we have achieved satisfactory cooling of the ventricles, the rate is reduced to 100 mL/min. We like to maintain a coronary sinus pressure of greater than 20 mm Hg to charge the venous system with enough pressure to perfuse the myocardium well. From this time on, the infused cardioplegia is only cold blood that is taken directly from the arterial line without any Normasol dilution or potassium added. No topical cooling is used. Many times, cardioplegia is stopped for a short period of time while the sewing of the anastomosis is completed.

Finally, when the procedure is almost completed, the cold retrograde cardioplegia is then turned off. At this time, the perfusionist disconnects and drains the cooling coils and empties the cool blood within the retrograde system. Rewarming has begun, and warming systemic blood is then brought into the retrograde system for our warm reperfusion dose. This begins in coronary cases after our final anastomosis has been completed. This dose is given at 300 mL/min for 5 minutes. Four millimoles of potassium is added initially, and then another 4 mmol is added after the first 2½ minutes of warm cardioplegia has

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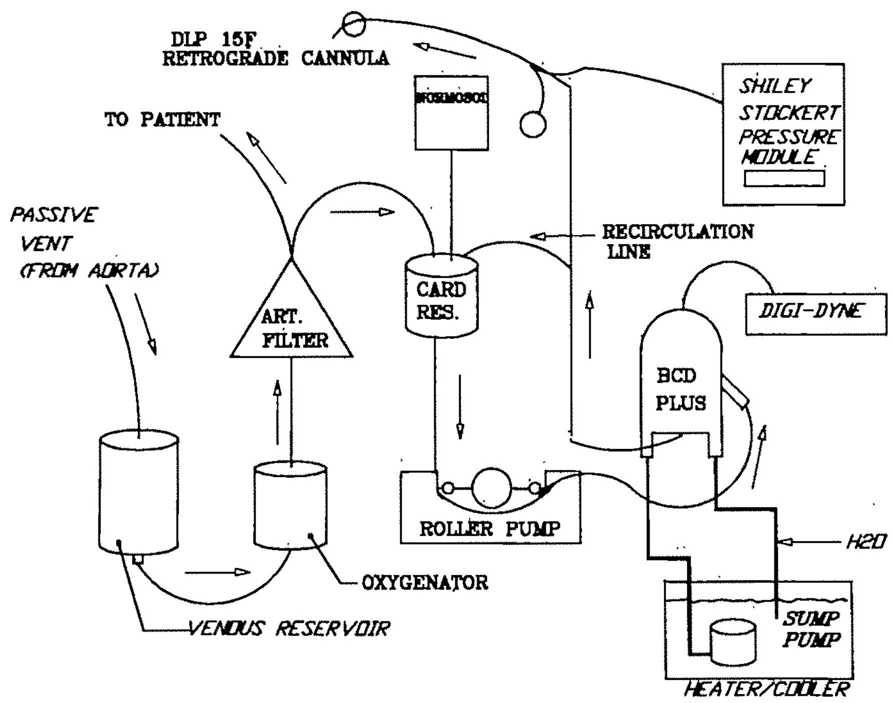

Fig 1. Cardioplegia circuit.

been given to keep the heart from fibrillating. Longer doses of warm reperfusion are given for longer cross-clamp times. The retrograde balloon is then deflated, and the cannula and cross-clamp are removed.

Comment

In the past year we have used this method of cardioplegia in 91% of our 446 open heart patients. This included 366 coronary artery bypasses and 80 valve procedures. Presently, we attempt to use retrograde cardioplegia in all cases and are successful 98% of the time. We have recently reported to *The Journal of Molecular and Cellular Cardiology* on 100 consecutive patients, ending December 31, 1989. This showed an operative mortality of 4%, a requirement of inotropic support greater than 24 hours in 16%, creatine kinase evidence of myocardial infarction in 4%, but clinical evidence of myocardial infarction in 1%. Thirty-four patients had postoperative evaluation of ejection fraction, and in all but 1 patient, the myocardial function was preserved or improved.

We have great confidence in this system and feel tremendous freedom to do all that is necessary without being a slave to the cross-clamp time. In our recent study, with a mean cross-clamp time of 87 minutes, we used an average of 6,408 mL of blood cardioplegia. For all this volume, the only amount of crystalloid added to the pump is the initial prime of the cardioplegia system (400 mL). No slush is used. Similarly, despite the large volume of cardioplegia, we generally use only 24 mmol of potassium. Although proximal anastomoses are done before the bypass is begun, we continue to use our warm reperfusion dose in a retrograde fashion because 99% of our patients have at least one internal mammary artery bypass graft, and clearly antegrade reperfusion would be suboptimal with this. We also feel strongly that during the reperfusion period the arterial endothelium should not be subjected to high pressure, and this is well avoided with the retrograde system, where we have high flow and low pressure. Finally, the beauty of this system is its relative simplicity in all aspects. The pump set up is simple, and the system is safe, because we have the coronary sinus pressure monitored, which prevents rupture of the sinus from overpressurization. The true advantage of this system is that the cardioplegia is for the most part 4°C continuous perfusion of 0.21 hematocrit blood without any additives, allowing a large amount of cardioplegia to be given by this technique without any extra volume going to the patient. We advocate this type of myocardial protection for all open heart procedures.

Table 1. Exsanguination Formula[a]

	Values	
Patient	x	y
Normal male	70	14.70
Obese male, normal female	65	13.65
Obese female	55	11.55

[a] Amount of autologous blood for collection =

$$[(x) \cdot kg] - 100 \cdot \frac{(y) \cdot kg + 0.21 \cdot PV}{Hct}$$

HCT = prebypass hematocrit; kg = patient's weight in kilograms; PV = priming volume of perfusion circuit.

Pleural Anesthetics Given Through an Epidural Catheter Secured Inside a Chest Tube

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Pain management after thoracic surgical procedures is a difficult clinical problem. A variety of pain management methods are used with variable efficacy. This paper presents an effective method of pleural anesthetic administration using a pleural catheter inserted through a chest tube.

(Ann Thorac Surg 1991;51:138–9)

Analgesia after thoracotomy, tube thoracostomy, or thoracic trauma may pose a difficult problem for the surgeon and the patient. A variety of analgesic methods are currently available including narcotic agents, patient-controlled analgesics, intercostal nerve blocks, and pleural anesthetic agents. Moderate- to long-acting local anesthetics (eg, bupivacaine) administered into the pleural space provide a safe and effective method of pain control in thoracic surgical patients [1, 2] as well as in abdominal surgical patients [3, 4]. This type of anesthetic administration may decrease narcotic requirements and, therefore, decrease narcotic side effects such as respiratory depression and paralytic ileus [5]. Pleural anesthetics do not require the multiple percutaneous injections with the risk of intravascular injection of anesthetic or of pneumothorax during the administration of intercostal nerve blocks. Pleural anesthetics can be administered either through an indwelling pleural catheter or through a chest tube. Pleural catheters maintain a closed sterile system preventing contamination and avoiding other mechanical problems associated with injections directly into chest tubes such as pneumothorax. Pleural catheters may be placed percutaneously during thoracotomy but can be difficult to position optimally. Likewise, placement during tube thoracostomy may be difficult owing to the small caliber and flexibility of the catheters. This paper describes a method of percutaneous placement of a pleural catheter through a chest tube, enabling safe, easy, and accurate catheter placement during thoracotomy or tube thoracostomy.

Technique

We use a standard epidural catheter insertion set and a standard chest tube. The epidural introducer needle is

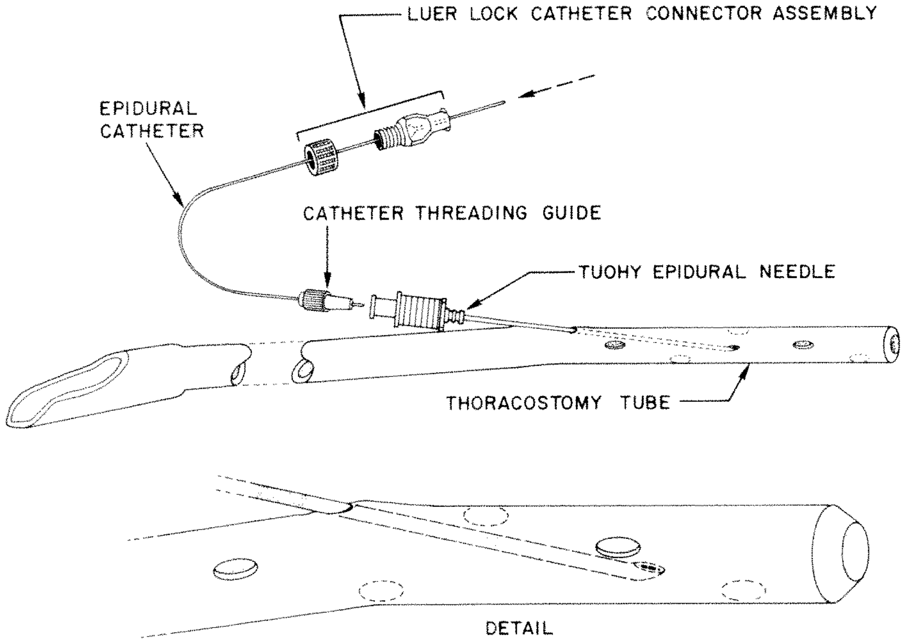

Fig 1. The catheter is advanced through the introducer needle, which is inserted through the side of the chest tube near the hole closest to the chest bottle. The tip of the catheter is positioned approximately 1 cm from the tip of the chest tube, then the introducer needle is removed. The Luer lock adaptor is then attached to the proximal end of the pleural catheter.

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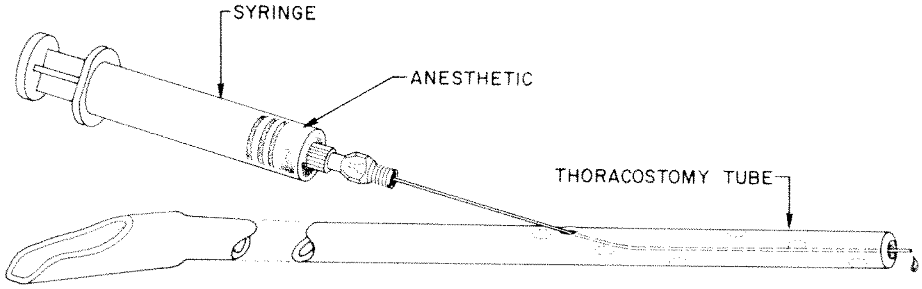

Fig 2. The assembly is placed directly during thoracotomy or percutaneously using standard tube thoracostomy techniques. The tip of the catheter is positioned posteriorly and at the apex. The catheter is firmly attached to the external portion of the chest tube with tape.

inserted through the side of the chest tube near the hole closest to the chest bottle. The epidural catheter is then inserted through the needle and advanced until its tip protrudes about 1 cm through the distal end of the chest tube (Fig 1). The combined assembly is then inserted percutaneously using standard tube thoracostomy techniques. If placed during an intrathoracic procedure, the catheter is inserted into the chest tube after the tube has been pulled through the chest wall. The entry site of the catheter into the chest tube should be positioned within the pleural space to prevent potential air leak. Ideally, the assembly should be positioned posteriorly within the pleural space.

After insertion, the pleural catheter can be secured to the chest tube with ¼-inch tape but not tied with the chest tube stitch. The pleural catheter is then fitted with a Luer cap that will allow injections directly through the rubber diaphragm (Fig 2). Local anesthetics are administered through the pleural catheter as needed. We use preservative-free 0.25% bupivacaine with epinephrine at 0.5 mL/kg every 6 hours as needed for pain. However, continuous infusion of local anesthetic agents may also be used [1]. The maximum safe dose of 0.25% bupivacaine with epinephrine is up to 1 mL/kg of body weight every 6 hours.

Comment

Pleural administration of local anesthetics is an effective method of pain management in patients undergoing thoracic surgical procedures including percutaneous tube thoracostomy [1, 2]. Administration requires either an indwelling pleural catheter or a chest tube. The former provides a closed system with maintenance of sterility and avoidance of mechanical problems associated with repeated injections directly into the chest tube. Pleural catheters can be placed directly during thoracotomy. Blind percutaneous placement may be difficult owing to the flexibility and the small caliber of these catheters. In addition, blind percutaneous placement carries a small risk of pneumothorax or lung injury [4]. The combination of pleural catheter and chest tube facilitates percutaneous placement and enables the surgeon to use pleural anesthetics in any patient requiring a chest tube. This system ensures good positioning of the catheter posteriorly and at the apex of the pleural space. It also prevents kinking or coiling of the pleural catheter, which may be a problem even with catheters placed during open thoracotomy. A closed sterile system without air leak is maintained. The catheter can also be securely attached to the chest tube, which helps avoid inadvertent removal. In our experience, efficacy is excellent and redosing is easy with use of a Luer lock adaptor. We have used this technique in more than 25 patients undergoing either thoracotomy or thoracostomy tube placement. Specific surgical procedures include posterolateral thoracotomy for pulmonary resections, tube thoracostomy for pneumothorax, and tube thoracostomy after transhiatal esophagectomy.

In our experience, there have been no complications attributable to the pleural catheter nor have there been any instances of cardiac or central nervous system problems caused by the anesthetics. We have observed that when this technique is used, the patients rarely require parenteral narcotics during the 4 to 6 hours after administration of the anesthetics.

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Intraoperative Coronary Angiography Using Fluorescein

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Intraoperative coronary angiography using fluorescein was applied to evaluate the patency of saphenous vein grafts just after completion of the distal anastomosis. By this technique, the area of the revascularized myocardium was well estimated in real time. This intraoperative direct-vision examination gives us more timely and precise information during coronary artery bypass grafting.

(Ann Thorac Surg 1991;51:140–3)

Intraoperative measurement of the amount of graft flow by magnetic flow meter is the only way to determine the area of revascularized myocardium and graft patency. To obtain more precise and direct information during coronary revascularization, a reliable intraoperative visual examination method is desirable. Intraoperative coronary angiography using fluorescein was applied for this purpose in 29 consecutive cases of coronary artery bypass grafting.

Methods

As a contrast medium, 3 mL of 10% fluorescein sodium was diluted with 500 mL of normal saline solution (0.06% fluorescein solution) and 5 mL of 0.7% sodium bicarbonate; 3 mL of heparin was added to adjust the pH and to keep the anticoagulability. A 6-W black fluorescent light bulb was used as the fluorescence-evoking source.

After the distal anastomoses using saphenous vein graft were performed, all lights in the operating room were turned off, and the fluorescent black light bulb was hung 10 cm over the heart to illuminate the cardiac wall. Then 20 to 40 mL of fluorescent contrast media was injected from the proximal end of the saphenous vein graft using a pressure of 150 mm Hg (Fig 1).

Results

In all cases, bright green-yellow fluorescence was clearly observed in real time in the following order: bypass graft, anastomosis, coronary artery, its branch, myocardial wall, and coronary vein. The revascularized area through the graft showed bright fluorescence in clear contrast with the nonperfused adjacent area. The distribution of the graft flow and the anastomotic state could be easily recognized by the naked eye. Prolongation of the aortic cross-clamp time by this examination was only 1 to 2 minutes.

In Figure 2, a saphenous vein graft was anastomosed to the left anterior descending artery (LAD). A large perfused area including the first and the second diagonal branches of the LAD was clearly observed.

Figure 3 shows the seqential bypass graft to the posterior descending branch of the right coronary artery and the posterolateral branch of the circumflex artery. The fluorescein perfused the inferior and lateral cardiac walls through two anastomoses, and it showed bright fluorescence with a clear border. The first diagonal branch of the LAD was also detected by collateral flow from the poste-

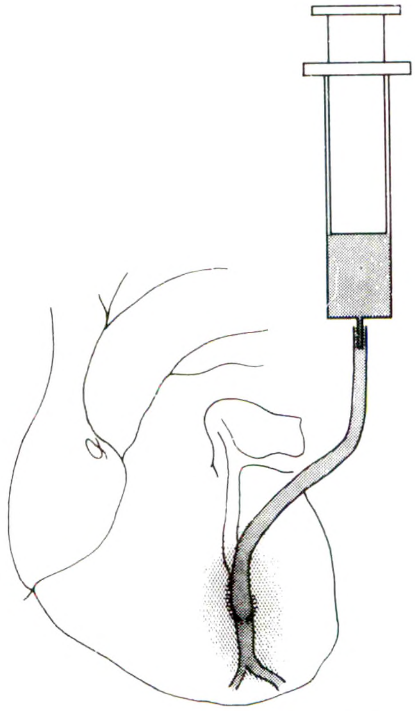

Fig 1. Schema of the examination method. The contrast medium was injected from the proximal end of the bypass graft.

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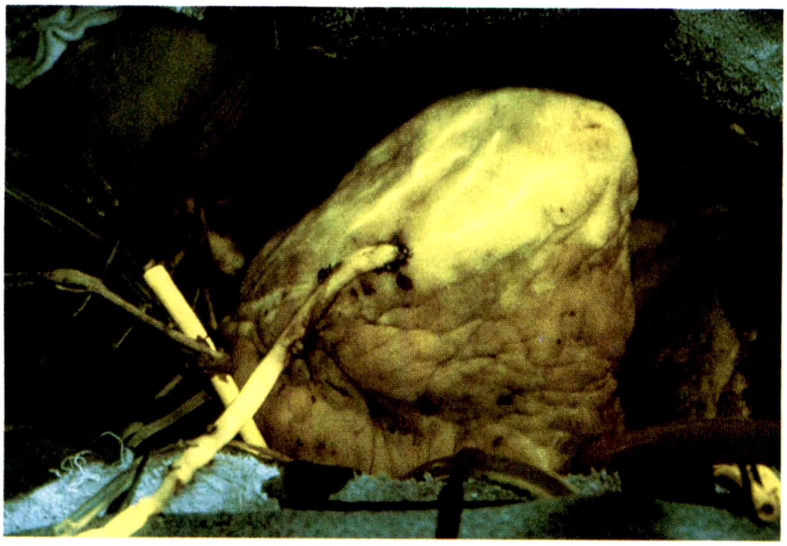
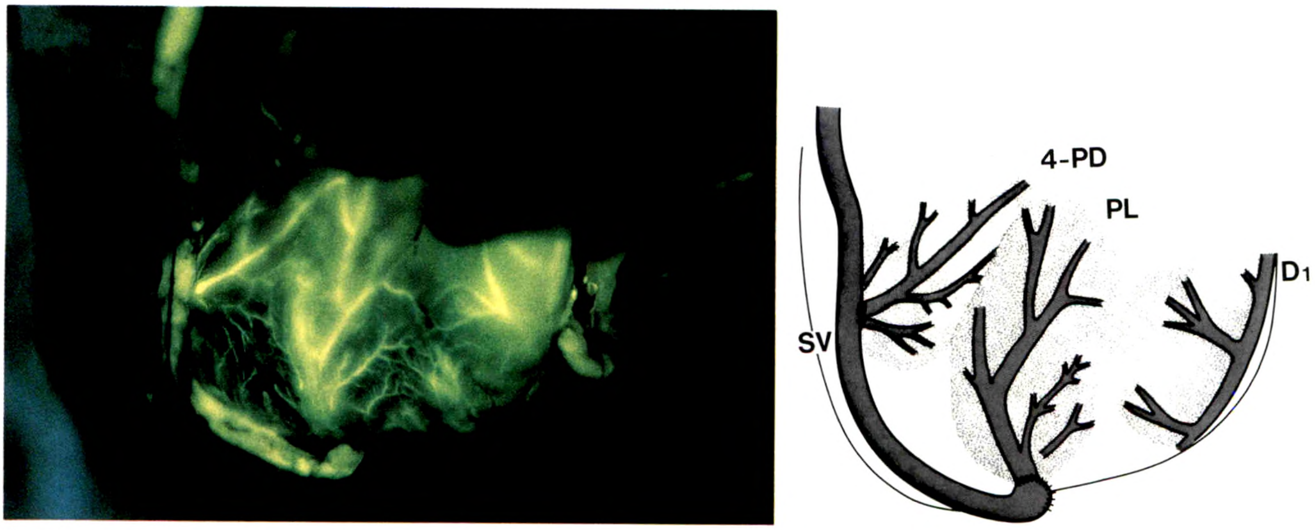


Fig 2. A large revascularized area including the diagonal branches from the bypass graft to the left anterior descending artery showed clear fluorescence.

rolateral branch. In Figure 4, the saphenous vein was anastomosed to the LAD just distal to the second diagonal branch. At fluorescein angiography, the diagonal branches were well visualized first by the retrograde flow from the anastomosis (Fig 4A), and the antegrade stream to the LAD was observed with delay (Fig 4B). Through these findings, the pronounced stenosis at the anastomosis was strongly suspected. Because the extent of the fluorescence at the LAD area finally seemed to be enough (Fig 4B), no additional procedure was performed. The flow volume of this bypass graft measured by the magnetic flow meter was 65 mL/min, and the postoperative course was quite uneventful without showing any ST change on the electrocardiogram. Through findings in postoperative coronary angiography as well as in intraoperative examination, the preferential flow to the diagonal branches and the more than 50% stenosis of the anastomosis were confirmed (Fig 5A, B).



A

B

Fig 3. (A) Sequential bypass grafting to the posterior descending artery from right coronary artery (4-PD) and the posterolateral branch of the circumflex artery (PL). Fluorescein perfused through both anastomoses and also through the area of the first diagonal branch (D_1) of the left anterior descending artery. (B) The schema. (SV = saphenous vein graft.)

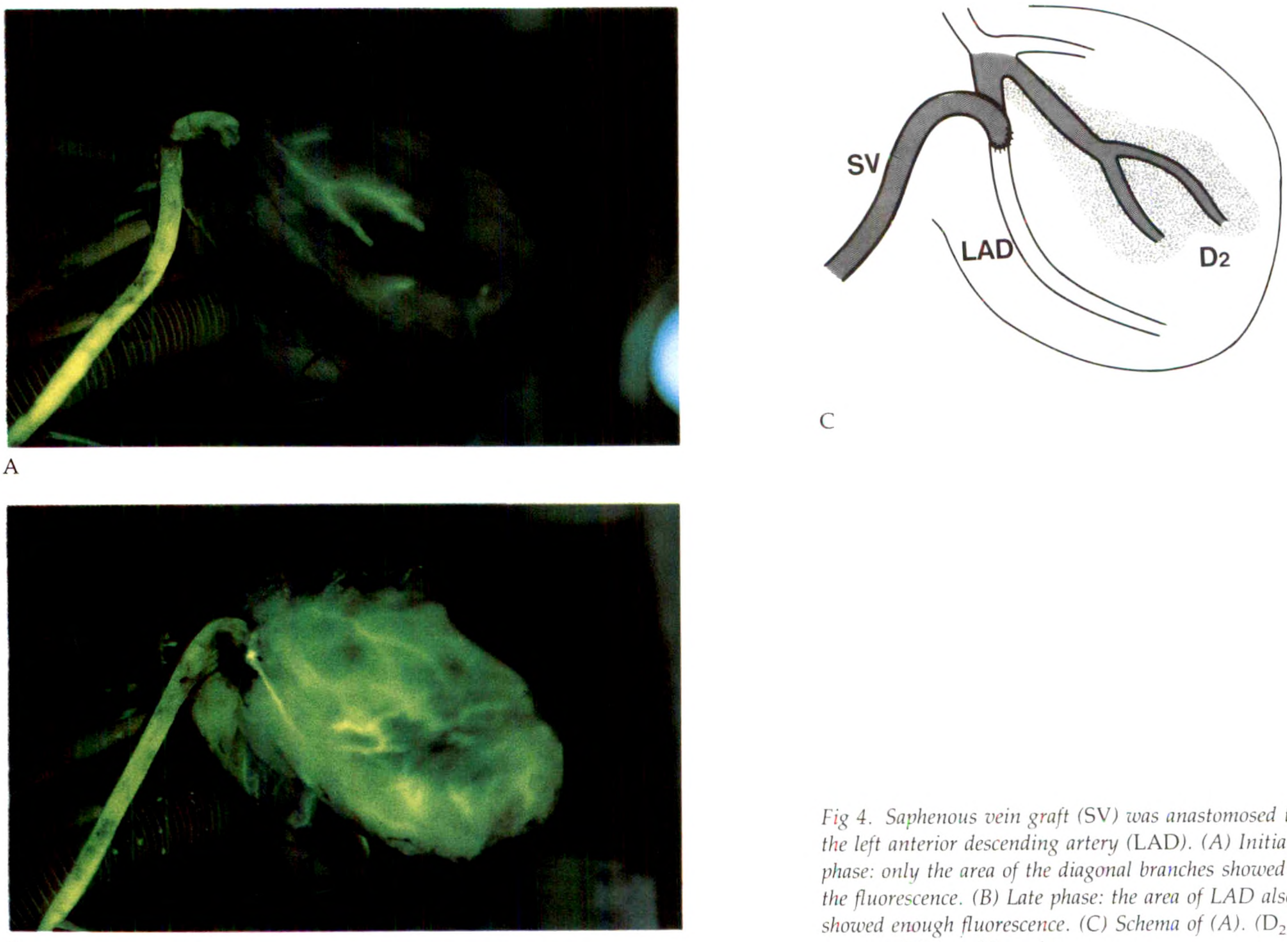


Fig 4. Saphenous vein graft (SV) *was anastomosed to the left anterior descending artery* (LAD). *(A) Initial phase: only the area of the diagonal branches showed the fluorescence. (B) Late phase: the area of LAD also showed enough fluorescence. (C) Schema of (A).* (D_2 *= second diagonal branch.)*

Comment

There is no other conventional method except magnetic flow meter to evaluate the surgical results intraoperatively in coronary artery bypass grafting. If the graft flow volume measured by magnetic flow meter is unexpectedly low, the question arises whether it is due to anastomotic stenosis or to poor peripheral run-off. Surgeons cannot get any information until postoperative coronary angiography is performed.

The results of intraoperative thermography [1] for this purpose are sometimes misunderstood owing to many kinds of artifacts such as cold saline solution used for topical cooling, cardioplegic solution, and the surgeon's finger. Furthermore, the necessity of special equipment makes this method unpopular.

Intraoperative coronary angiography using fluorescein was performed for indirect myocardial revascularization by Armellini and colleagues [2], but it was not applied to visualize directly the coronary arteries. Through our method, exact quantitative evaluation of the stenosis such as given by coronary angiography was difficult but enough clinical information as to whether the stenosis of the anastomosis is critical or whether the distribution of the graft flow is normal could be obtained by observing the passage and smoothness of the fluorescent stream through the anastomosis.

The safety of the fluorescein has been fully studied in the field of the ophthalmography [3]. Sodium bicarbonate was added to the contrast media to adjust the pH between 7.0 and 9.0, at which fluorescein showed best contrast. The 6-W fluorescent black light evoked enough fluorescence from the contrast medium. Application of this method is now limited to the vein graft because of the difficulty of finding feasible access for the fluorescein injection into arterial grafts.

In conclusion, this technique was quite easy and reproducible within a minimum time without any special equipment. We believe intraoperative coronary angiography using fluorescein is a useful and practical examination for performing more precise coronary artery bypass grafting.

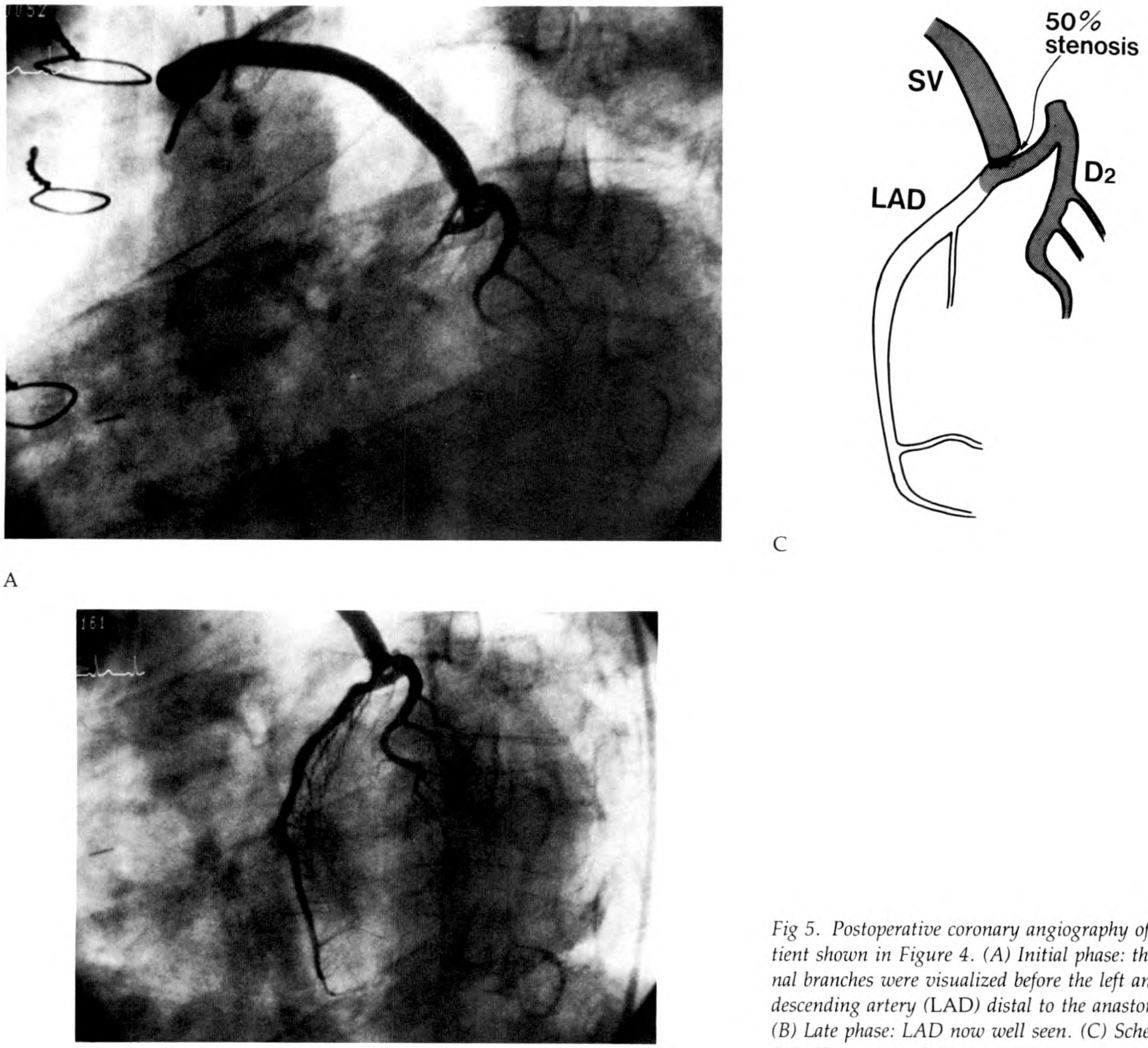


Fig 5. Postoperative coronary angiography of the patient shown in Figure 4. (A) Initial phase: the diagonal branches were visualized before the left anterior descending artery (LAD) *distal to the anastomosis. (B) Late phase: LAD now well seen. (C) Schema of (A).* (D_2 = *second diagonal;* SV = *saphenous vein graft.)*

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Alternative Technique for Repair of Sinus Venosus Atrial Septal Defect

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A technique is described for closure of a sinus venosus atrial septal defect using a single patch held in place by sutures placed from outside the right atrium and underneath the superior vena cava. The superior vena cava does not require enlargement and potential damage to the artery to the sinoatrial node is avoided.

(Ann Thorac Surg 1991;51:144–6)

Since the paper by Neptune, Bailey, and Goldberg [1] in 1953 many ingenious surgical techniques have been described for the redirection of anomalous pulmonary venous drainage from the right lung through a sinus venosus atrial septal defect (ASD) high in the atrial septum. These have included single patches, an inner and outer patch, a U-shaped patch, direct partitioning of the superior vena cava (SVC), and various rotational flaps of right atrial wall [2]. The diagnosis of a sinus venosus defect is occasionally not made preoperatively, the surgeon expecting a straightforward secundum ASD. Closure of a secundum ASD is often considered to be part of general cardiac surgery and thus may be undertaken by surgeons who are not experienced in the surgery of congenital defects. It is for this reason that we describe a simpler technique of dealing with the sinus venosus ASD that we have found applicable to all variations of anatomy.

Material and Methods

Over a 10-year period 54 patients (22% of all ASD closures) had repair of a sinus venosus ASD using the technique described here. Median age was 9 years with a range of 1 to 58 years.

All operations were performed by a median sternotomy incision, and cardiopulmonary bypass was established using caval cannulas (introduced by the right atrial appendage and the low right atrium, respectively) and caval snares, hypothermia to 32°C, and cold crystalloid potassium cardioplegia.

Figure 1 illustrates the oblique right atriotomy beginning at the base of the atrial appendage and extended down toward the inferior vena cava staying well away from both the sinoatrial node and the SVC–right atrial junction. Exposure is aided by retracting the SVC cannula, and horizontal buttressed mattress sutures are placed from outside the heart along the junction between the anomalous right pulmonary veins and the right atrium. Superiorly these sutures are continued medially, passing from outside the heart underneath the SVC, avoiding the artery to the sinoatrial node if this is visible; the sutures are placed in such a way as to avoid narrowing the SVC.

Figure 2 illustrates the placement of these sutures through the patch material (over the time period we used xenograft pericardium, Dacron, or Gore-Tex). After placement of the sutures, the patch is slid down into position. If the ASD requires enlargement, this is done inferiorly and then the inferior rim of the patch is sewn to the edge of the septal defect using either interrupted or continuous sutures. In this way the SVC is not narrowed and the anomalous pulmonary venous drainage is directed into the left atrium. Exposure of the top end of the defect, if it extends up into the SVC, is facilitated by retraction on the individual sutures as they are placed. Although the right pulmonary veins drained into the SVC itself in 8 of the 54 patients, enlargement of the SVC was never necessary.

Results

There was one death in the perioperative period from complications unrelated to the surgical technique. In the early postoperative period 7 patients had episodes of nodal rhythm and 1 went into atrial fibrillation.

In the late follow-up the patient with early postoperative atrial fibrillation remains in atrial fibrillation, and 1 patient has continuing nodal rhythm. There have been no cases of either SVC or pulmonary venous obstruction documented in the follow-up period, which now extends longer than 10 years.

Comment

Kyger and associates [3] described an incidence of new postoperative arrhythmias of 21% in 109 patients. All the surgical techniques described previously involve an incision across the junction of the SVC and right atrium, and even if this avoids the sinoatrial node the arterial supply to the node itself may be divided if the artery passes

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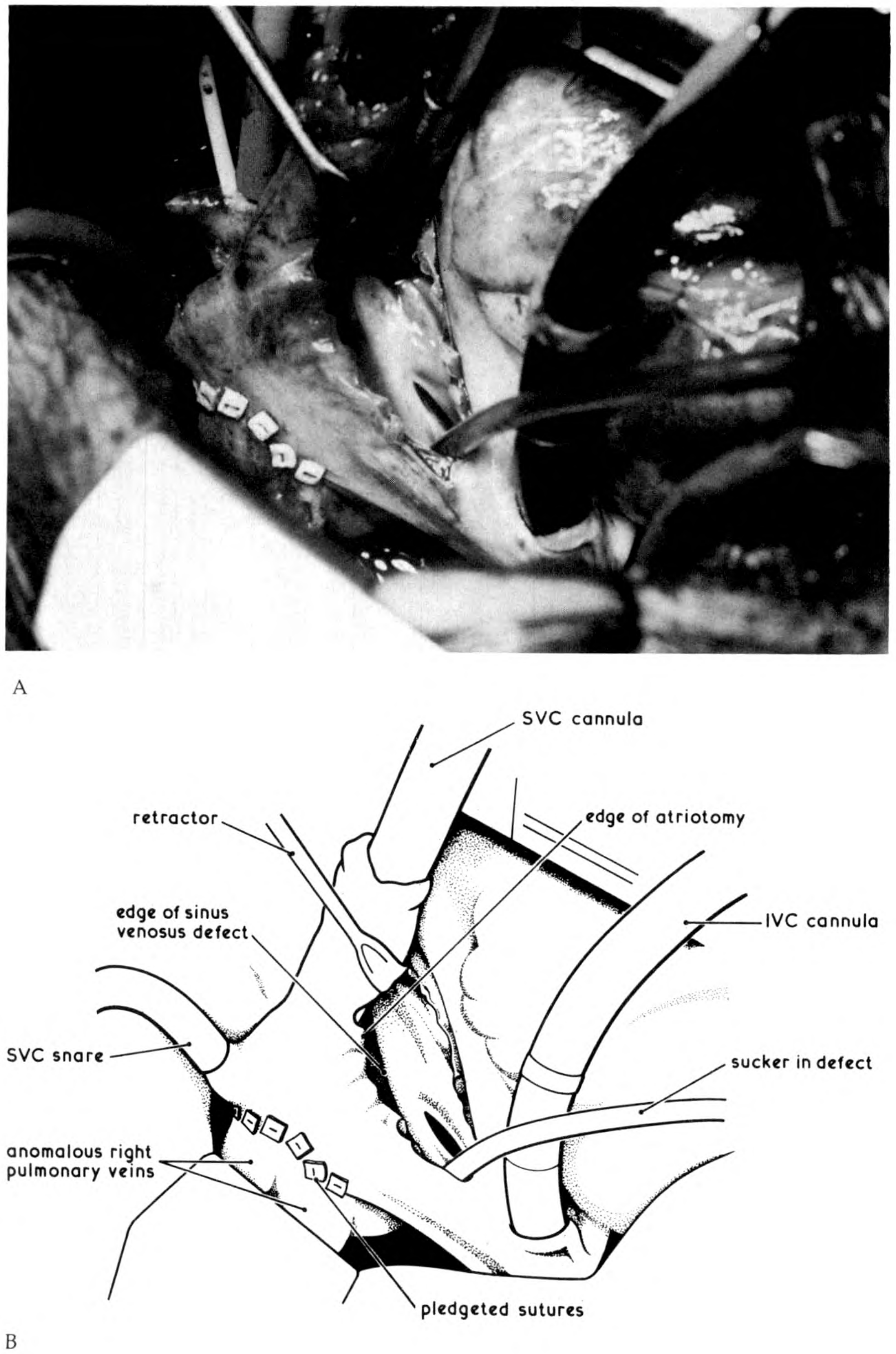
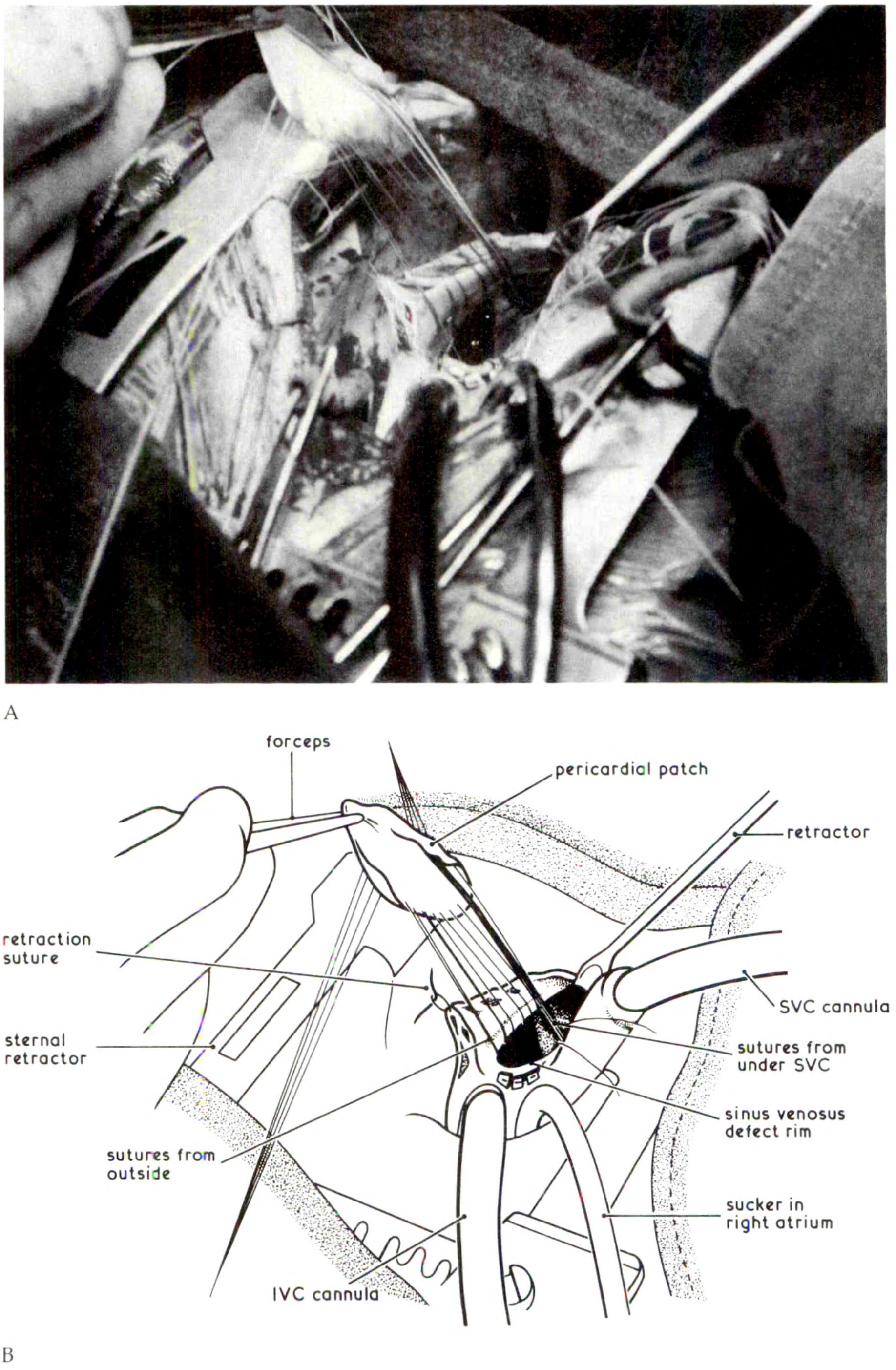


Fig 1. (A) Operative photograph taken from the surgeon's view and (B) drawing showing the right atriotomy distant from the sinoatrial node and buttressed sutures and separating the anomalous right pulmonary veins from the right atrium. (IVC = *inferior vena cava;* SVC = *superior vena cava.)*

behind the SVC to reach the node laterally. Although our incidence of postoperative arrhythmias is low it would be unrealistic to claim this is solely because of the surgical technique. However, the right atrial incision employed in our method does avoid damage in any way to the sinoatrial node. We believe an important feature of this method is its simplicity and that it will be particularly valuable to surgeons encountering a sinus venosus defect unexpectedly. The absence of any long-term problems with either systemic venous or pulmonary venous obstruction lead us to believe that the more complex maneuvers described in the literature are unnecessary.

We are grateful to Anna Durbin, Department of Medical Illustration, Leeds University, for producing the line diagrams from the operative photographs. We are also grateful to Hannah Warren for her help in preparing the manuscript.

Fig 2. (A) Operative photograph taken from the assistant's position (patient's left) and (B) drawing showing the sutures coming to the patch from outside the heart both on the patient's right and left (from under the superior vena cava (SVC). The patch is about to be slid into position. (IVC = inferior vena cava.)



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Christiaan Barnard's Contribution to the Surgical Treatment of Ebstein's Malformation

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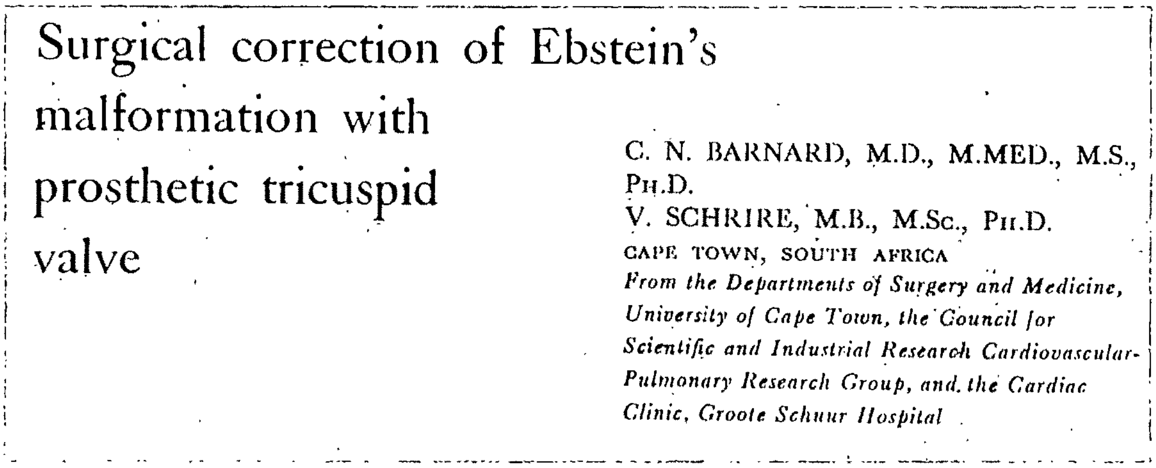
The University of Alabama at Birmingham, Birmingham, Alabama

The pioneering surgical endeavors of Christiaan Barnard in human cardiac transplantation are well recognized. His contribution in the surgery of Ebstein's malformation has also been unique. In 1963, Barnard's classic paper on "Surgical correction of Ebstein's malformation with prosthetic tricuspid valve" presented his pioneering accomplishments in this complex cardiac malformation.

(Ann Thorac Surg 1991;51:147–51)



Surgical correction of Ebstein's malformation with prosthetic tricuspid valve

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Ebstein's malformation is a rare congenital cardiac anomaly in which there is abnormal downward displacement of the septal and/or posterior tricuspid leaflets into the right ventricle. The presence of an atrial septal defect, the frequently severe tricuspid valve incompetence, and often debilitating supraventricular arrhythmias (occasionally associated with Wolff-Parkinson-White syndrome) produce the clinical syndromes in Ebstein's malformation that may require surgical intervention. In their classic 1963 publication [1], Barnard and Schrire clearly outlined in 2 case reports the classic indications for tricuspid valve operation in Ebstein's malformation.

The first patient was a 2½-year-old boy with refractory right-sided heart failure and persistent cyanosis. At operation, the patent foramen ovale was closed and the severely malformed and incompetent tricuspid valve was excised. A low-flow University of Cape Town lenticular prosthesis molded in Ivalon was inserted. The second patient was a 25-year-old man who had refractory right-sided heart failure and atrial dysrhythmias. He also underwent successful tricuspid valve replacement with a similar prosthetic valve. The atrial septum in this patient was intact. In both instances, Barnard and Schrire emphasized the importance of placing the valve sutures on the atrial side of the coronary sinus to avoid injury to the atrioventricular node and His bundle. They speculated that the "atrialized" right ventricle would not interfere with right ventricular output and correctly concluded that no adverse effects would result from coronary sinus blood draining directly into the right ventricle.

The natural history of Ebstein's malformation is highly variable. When symptoms are present early in life, such as in the first patient reported by Barnard and Schrire, there is frequently severe cyanosis associated with an interatrial communication, marked right-sided congestive heart failure resulting from severe tricuspid incompetence and occasional stenosis, and marked cardiomegaly [2]. The survival in this group is poor. The majority of patients, however, do not have symptoms until childhood or early adulthood, frequently with mild dyspnea and easy fatigability. About 60% of patients in whom symptoms develop after the neonatal period survive 20 years or more [3], and more than half the patients greater than 25 years of age with Ebstein's malformation are in New York Heart Association class I or II [4].

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Morphology

The morphology of Ebstein's malformation was lucidly described in Barnard and Schrire's classic article on tricuspid valve replacement. They clearly appreciated the great variability of this complex malformation and specifically referred to the anatomic details and surgical implications of the atrial septal defect, the tricuspid valve malformation, right ventricular size, the possibility of right ventricular outflow obstruction, and the potential physiologic consequences of the atrialized portion of the right ventricle. They also referred to the important morphologic abnormalities of the tricuspid valve itself, many of which have direct relevance for successful tricuspid valve reconstruction [5]. There is downward displacement of the septal and posterior leaflets into the right ventricle. The anterior leaflet is large and "sail-like," which is necessary for a competent valve after reconstruction. There may be important interchordal space obliteration and adherence to the right ventricular wall, which may create some degree of tricuspid stenosis. The tricuspid annulus is usually enlarged. An atrialized portion of the right ventricle is present between the tricuspid annulus and the attachment of the septal and posterior leaflets, which may be aneurysmal and move paradoxically with right ventricular contractions.

The diagnostic methodology for delineation of anatomic detail in Ebstein's malformation has gradually evolved since Barnard and Schrire's original report, which described the electrocardiographic, phonocardiographic, and angiocardiographic details. Currently two-dimensional echocardiography is particularly useful in elucidating the subtleties of tricuspid valve morphology that must be understood if valve reconstruction is planned [5–7].

Management of the Tricuspid Valve in the Surgical Treatment of Ebstein's Malformation

When operation is advised for Ebstein's malformation, the optimal management of the tricuspid valve and the atrialized portion of the right ventricle remain controversial in the current era, partly because of the variability of the tricuspid valve in this malformation, partly due to the limited experience gained by any one surgical group, and partly because of the delayed emergence of enthusiasm for reconstruction of the atrioventricular valves.

Tricuspid valve replacement has been the preferred management of the incompetent tricuspid valve of Ebstein's malformation in some institutions [8]. Barnard and Schrire's original article describes the method that has become standard for tricuspid valve replacement in this entity. During implantation of the prosthetic valve, the suture line is brought posterior to the coronary sinus and atrioventricular node near the junction between the displaced septal leaflet and the anterior leaflet. In other areas, the suture line follows the actual tricuspid valve annulus (Fig 1) [1, 9].

Based on a concept put forth by Hunter and Lillehei [10], Hardy and colleagues [11] reported successful correction of Ebstein's malformation with tricuspid reconstruction in a 42-year-old woman. Hardy and colleagues emphasized the importance of obliterating the atrialized portion of the right ventricle by "transposing" the displaced septal leaflet to the normal plane of the tricuspid valve and reducing the annular circumference.

In the current era, Danielson and his colleagues at the Mayo Clinic have generated a large experience in valve reconstruction (Fig 2) as part of the repair of Ebstein's malformation [12]. They emphasized a standard surgical approach including (1) electrophysiologic localization of accessory bypass tracts in patients with ventricular preexitation, (2) closure of the atrial septal defect, (3) plication of the atrialized portion of the right ventricle, (4) plastic repair or replacement of the tricuspid valve, (5) correction of associated cardiac anomalies, and (6) excision of redundant right atrial wall. They reported tricuspid valve reconstruction in 81% of patients (n = 42) with a hospital mortality of 7%. Danielson and colleagues' modification of Hardy and colleagues' [11] original description further underscored the importance of staying anterior and to the right of the coronary sinus with the annuloplasty sutures to avoid injury to the conduction system.

More recently, Carpentier and colleagues [5] have reported a different method of reconstruction employing a longitudinal plication of the atrialized chamber with detachment and repositioning of the displaced portion of the tricuspid annulus (Fig 3). Carpentier and colleagues addressed the variability of this malformation by recommending modification of the basic repair depending on the details of tricuspid valve and right ventricular morphology:

If the anterior leaflet is large and mobile without obliteration of interchordal spaces and with moderate displacement of the posterior and septal leaflets, a small atrialized chamber, and "adequate" right ventricular volume, then a plication of the annulus and adjacent right atrial wall is performed and the atrialized chamber is not plicated. A portion of the anterior and posterior leaflets is detached and repositioned at the level of the tricuspid annulus with additional support provided by a ring.

If the displacement of the leaflets is more extensive, with a large, thin, noncontractile atrialized portion and small right ventricle, then the atrialized chamber is obliterated with a longitudinal plication.

If there is restricted motion of the anterior leaflet with fibrous attachments to the right ventricle and obliteration of interchordal spaces, then extensive mobilization of the anterior leaflet, resection of fibrous bands, and fenestration of interchordal spaces is recommended before repositioning of the leaflets.

Late Surgical Results

Comparisons of the efficacy and durability of the various methods of managing the tricuspid valve in this entity have been confounded by the rarity and variability of this condition. After Barnard and Schrire's classic first description of tricuspid valve replacement, numerous authors [8, 13–15] have reported small series of such treatment. At

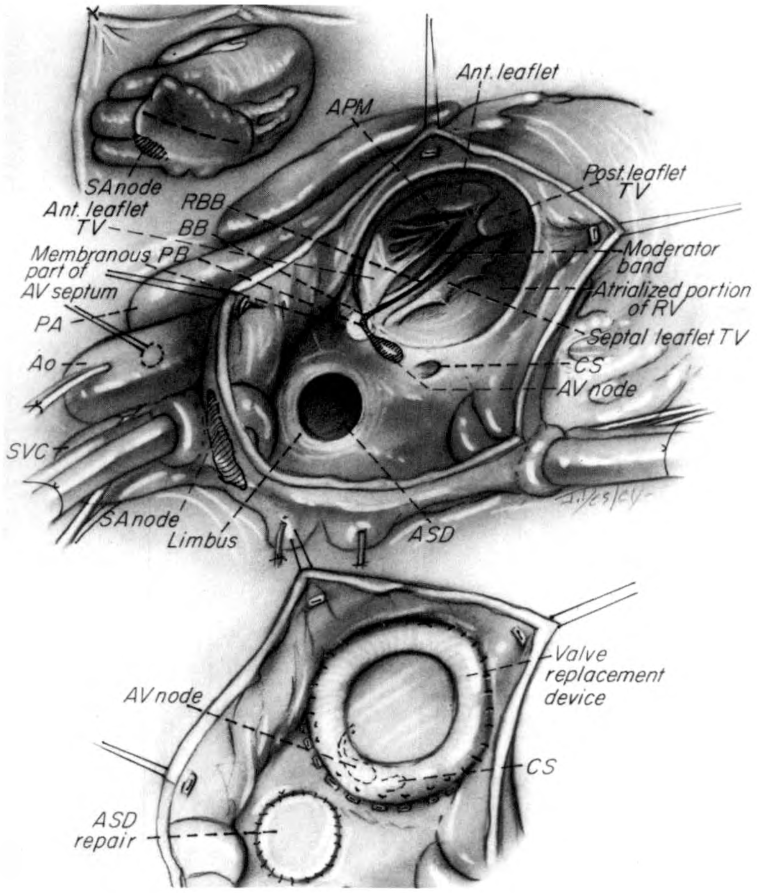

Fig 1. Replacement of the tricuspid valve and closure of the atrial septal defect in Ebstein's malformation, as originally described in Barnard and Schrire's historic article [1]. With exposure through an oblique right atriotomy, the downward displacement of the septal and posterior leaflets is illustrated, and the atrioventricular node is indicated adjacent to the commissure between the septal and anterior leaflets. The sutures for valve replacement are placed well posterior to the coronary sinus and membranous system. The remainder of the suture line then follows the actual tricuspid annulus. (Reproduced with permission from Bharati S, Lev M, Kirklin JW. Cardiac surgery and the conduction system. New York: Churchill Livingstone, 1983:3.46.)

The University of Alabama at Birmingham, for example, 24 patients underwent operation for Ebstein's malformation over a 14-year period, of whom only 16 had tricuspid valve replacement [8]. In one of the largest experiences, Mair and colleagues [16] from the Mayo Clinic reported 72 patients undergoing operation over a 12-year period, 80% undergoing tricuspid valve reconstruction. Carpentier and colleagues [5] repaired the tricuspid valve in 13 of 14

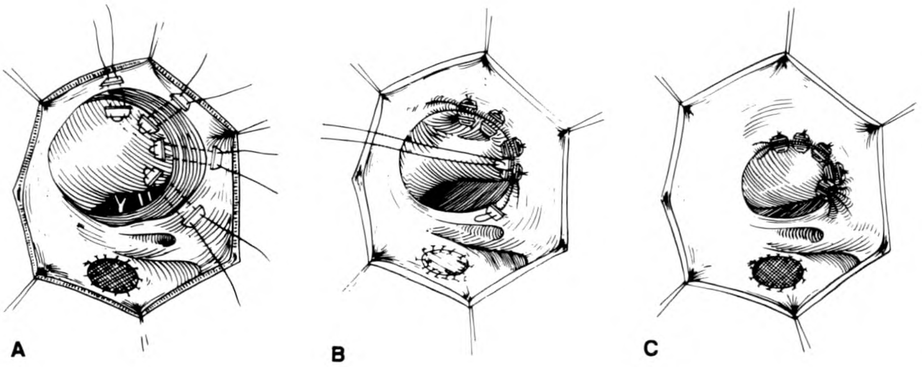

Fig 2. Annuloplasty repair of tricuspid valve in Ebstein's malformation, as described by Danielson and Fuster [12]. (A) The atrialized portion of the ventricle is plicated with interrupted pledgeted mattress sutures (shown from the surgeon's viewpoint, with the patient's head to the left). The atrial septal defect has been closed with a patch. (B) An annuloplasty suture is placed to narrow the tricuspid annulus and includes the entire posterior leaflet. The coronary sinus marks the posterior and leftward extent of the annuloplasty, avoiding the area of the conduction system. (C) The completed repair allows the large anterior leaflet to function as a monocusp valve. (Reproduced with permission from Danielson GK, Fuster V. Surgical repair of Ebstein's anomaly. Ann Surg 1982;196:499–504.)

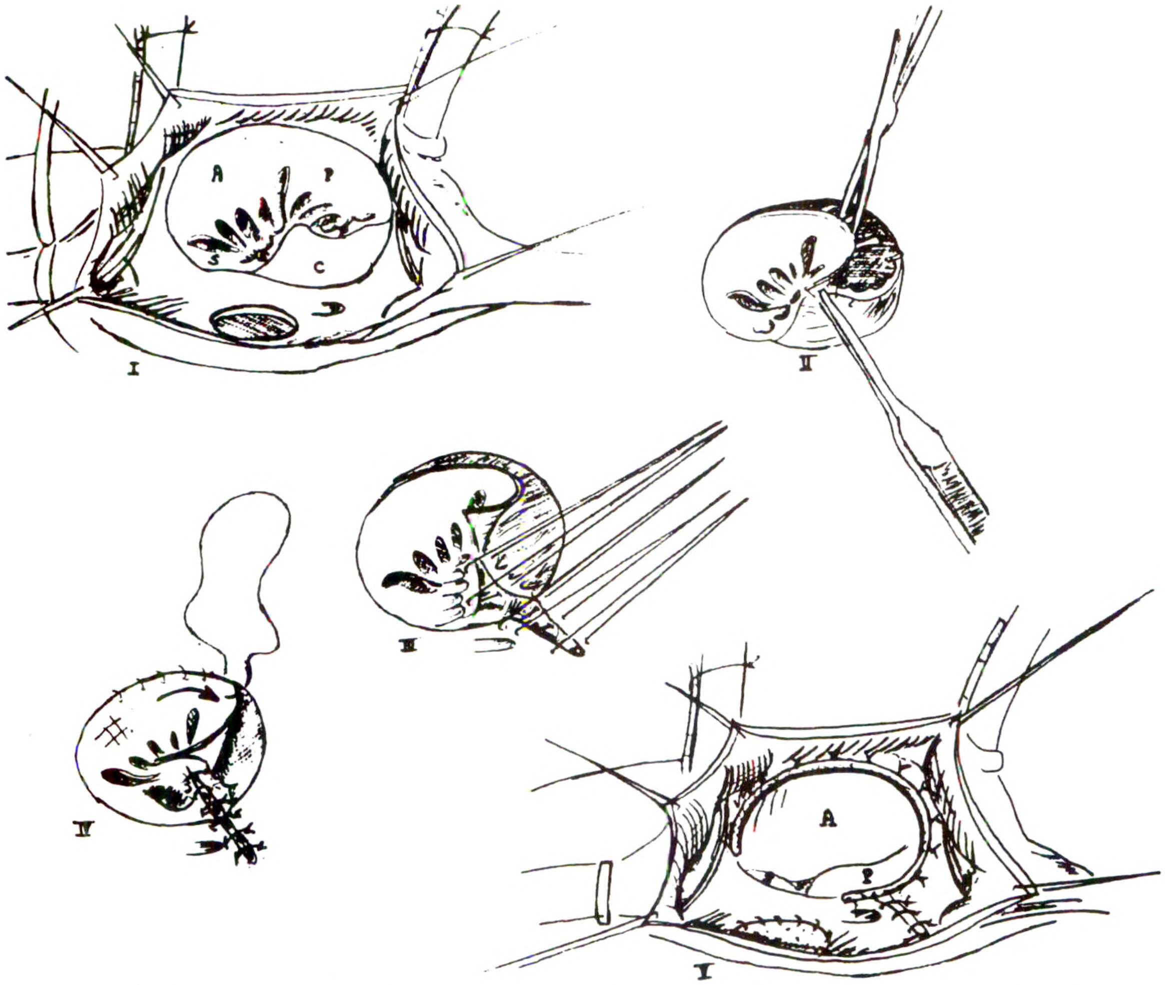

Fig 3. Tricuspid valve repair using a longitudinal plication, as described by Carpentier and associates [5]. (I) Surgeon's view. (II) Anterior leaflet and adjacent posterior leaflet are detached from the annulus. (III) Longitudinal plication of right ventricle, tricuspid annulus, and right atrium. (IV) Anterior and posterior leaflets are sutured to tricuspid annulus after clockwise rotation. (V) Prosthetic ring is inserted to reinforce repairs. Atrial septal defect is closed with a patch. (A = *anterior leaflet;* P = *posterior leaflet;* S = *septal leaflet.*) *(Reproduced with permission from Carpentier A, Chauvaud S, Mace L, et al. A new reconstructive operation for Ebstein's anomaly of the tricuspid valve. J Thorac Cardiovasc Surg 1988;96:92–101).*

patients operated on for Ebstein's malformation over a 6-year period.

The intermediate-term results after tricuspid valve replacement as part of the corrective operation are generally good, with most patients remaining in NYHA class I or II after 2 to 10 years [8, 14, 16]. The choice of prosthesis (heterograft or Starr-Edwards valve) has not made an apparent difference in long-term results. In the experience of Mair and associates [16] and Carpentier and colleagues [5], at a mean follow-up of 3 to 5 years, greater than 80% of patients remain in NYHA class I or II after valve reconstruction. The vast majority of patients reported by these two groups have normal valve function with minimal incompetence on follow-up two-dimensional echocardiographic studies.

In general, patients undergoing tricuspid valve replacement or repair as part of the correction of Ebstein's malformation experience an increase in exercise tolerance [17], decrease in cardiothoracic ratio [16], and normalization of systemic arterial oxygen saturation [17]. Late survival is generally good after tricuspid valve repair or replacement, but occasional late deaths occur, usually in the setting of persistent severe atrial (non–Wolff-Parkinson-White) or ventricular arrhythmias in patients with advanced (class IV) heart failure preoperatively [8].

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Editor's Note

We asked Professor Barnard to comment on Dr Kirklin's article.

Prof Barnard's Commentary

I thank you for sending me this article by Jim Kirklin.

As soon as I received your letter I visited the Cardiac Clinic to find out what happened to the first patient that we treated in this manner. I was very happy to find out that he was still alive and doing very well without any medical treatment. This is now nearly 28 years since the operation. It must be one of the longest implantations of a prosthetic valve in the tricuspid area.

Prof C. N. Barnard

Thymoma: Results of 241 Operated Cases

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Clinical and histopathological aspects of 241 thymomas were reviewed. One hundred sixty of the patients with thymoma had myasthenia gravis and 15 had other autoimmune diseases; 55% of the thymomas were encapsulated and 45% invasive. Operation was radical resection in 87.5% of the patients, subtotal resection with residual tumor in 8.7%, and simple biopsy in 3.7%. A tumor relapse was observed in 24 patients (10%): 2 (1.5%) of 133 with encapsulated thymomas and 22 (20.4%) of 108 with invasive thymomas; among these patients, a relapse was found in 20.6% of the patients who received radiotherapy postoperatively and in 24.6% who did not. Adverse prognostic factors were clinical stage IVa (multiple pleural nodes), not feasible resection (for technical reasons), inoperable tumor relapse, and association with one of the following autoimmune diseases: pure red cell aplasia, hypogammaglobulinemia, and lupus erythematosus. Conversely, myasthenia gravis is now a curable disease; it contributes to early discovery of associated thymoma, thus allowing a better survival for patients with thymoma who have myasthenia gravis compared with patients with thymoma but without myasthenia gravis ($p <$ 0.05). Postoperative radiotherapy does not seem necessary after removal of encapsulated thymomas, but it is advisable in case of invasive thymomas, regardless of the extent of the resection.

(Ann Thorac Surg 1991;51:152–6)

Despite an impressive number of studies, many aspects of the pathophysiology and treatment of thymomas have not been clearly defined yet. In addition, the unique association with specific autoimmune diseases, notably myasthenia gravis (MG), represents a further source of difficulty in the interpretation of the results. Malignancy of thymomas has been definitely demonstrated and has been discussed with regard to invasiveness of surrounding tissues and to histology [1, 2]. Therefore, most centers advocate the most complete resection possible, including the tumor, the thymus gland, and the surrounding fatty tissue as well [3]; the appropriate use of neoadjuvant or adjuvant therapy (particularly radiotherapy and/or chemotherapy) is still controversial [4]. Simple transsternal versus a more extended operative approach, the treatment of recurrences [5, 6], and the use of adjuvant plasmapheresis constitute additional items of controversy.

The present retrospective study reports our experience with 241 consecutive operated thymomas to assess the most significant prognostic factors and the most appropriate therapeutical strategy.

Material and Methods

From 1959 to 1988, 241 consecutive patients with thymoma underwent operation at the Department of Thoracic Surgery of the University of Torino; there were 107 male and 134 female patients, ranging in age from 16 to 76 years with a mean age of 47 years.

Thymoma was defined as a tumor originating from the epithelial cells of the thymus [7]. Granulomatous masses (such as Hodgkin's disease), carcinoids, seminomas, lymphomas, and thymolipomas were excluded from the study.

Associated diseases were myasthenia gravis (MG) in 160 patients (half of whom had a roentgenographically detectable tumor), pure red cell aplasia in 7, hypogammaglobulinemia in 2, and lupus erythematosus in 6. The tumor was asymptomatic and discovered after a routine chest roentgenogram in 31 patients; in 6 patients a superior vena cava syndrome was present due to the extent of the neoplasm.

The surgical approach used was different for the patients with and without MG. In the former group we preferred a median longitudinal sternotomy (partial or total depending on the extent of the tumor), which allows us to remove both the thymoma and the thymus gland. In the patients without MG sternotomy was less used (44% of patients), and we used thoracotomy when the mass was omolateral.

Complete resection of the thymoma and the thymic gland, including perithymic fat tissue if tumor invasion was apparent or suspected, was carried out in 152 patients (95%) with and 59 patients (72.8%) without MG. Five patients with and 16 without MG underwent subtotal resection. A simple biopsy was the only surgical procedure in 3 myasthenic and 6 nonmyasthenic patients.

The method of surgical-pathological staging proposed by Masaoka and associates [8] was used to indicate the extent of tumor invasion at operation. Five stages were defined as follows: stage I: no capsular invasion; stage II: capsular or pleural invasion; stage III: invasion of surrounding tissues such as lung, pericardium, superior

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Table 1. Distribution of Surgical-Pathological Stages

Myasthenia Gravis	Stage			
	I	II	III	IVa
Present	88	28	36	8
Absent	45	6	17	13

vena cava, and aorta; stage IVa: dissemination in the thoracic cavity; and stage IVb: distant metastases. Histologically, we adopted the classification of Verley and Hollman [9] into four types: spindle cell, lymphocyte-rich, epithelial-rich, and undifferentiated, according to the ratio of lymphocytes to epithelial cells and the cell shape. Table 1 summarizes the surgical-pathological staging in the presence or absence of MG. A greater percentage of patients without MG had stage IVa tumors, as compared with MG patients. Possibly, the tumor may have been detected earlier in these patients because of the clinical surveillance of MG. Table 2 indicates the histological classification of the tumor in relation to the presence or absence of MG.

Survival rates were computed by the actuarial life-table method and the curve differences were tested using the log-rank test. A probability value less than 5% was regarded as significant.

Results

Fifty-two of 241 patients (21.6%) died. Seven patients died in the postoperative period, 5 of whom died of MG crises. Death caused by tumor occurred in 2 of 160 patients (1.2%) with and in 11 of 81 patients (13.6%) without MG. Other causes of death were MG crises in 14 patients, associated autoimmune diseases in 10, and unrelated causes in 9. The results were analyzed in terms of the presence or absence of MG. Follow-up was conducted in 234 patients, with a minimum follow-up time of 2 years (mean, 10 years).

Overall Survival and Survival With and Without Myasthenia Gravis

The overall survival curve shows that 80.8% of the patients are alive at 5 years and 75.6% at 10 years. The comparison between the patients with and without MG establishes that survival rates are higher in the presence of MG ($p < 0.05$) (Fig 1).

Table 2. Distribution of Histological Types

Type	With MG	Without MG	Total
1 (Spindle cell)	6	11	17
2 (Lymphocyte-rich)	49	19	68
3 (Epithelial-rich)	102	48	150
4 (Undifferentiated)	3	3	6

MG = myasthenia gravis.

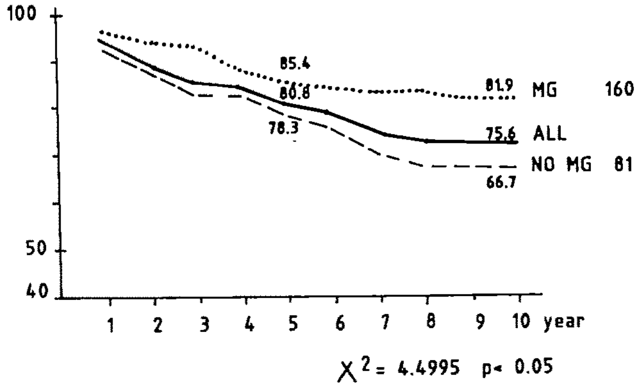


Fig 1. Overall 5-year and 10-year survival and survival according to the presence or absence of myasthenia gravis (MG).

Survival by Patient Age

Survival rates were calculated by grouping the patients in four age classes: 15 to 30 years, 31 to 45 years, 46 to 60 years, and more than 60 years. Although survival gradually decreases with age, as expected in a normal population distribution, the differences among the four groups are not significant. It is unlikely, therefore, that thymomas become more aggressive with age.

Survival by Histological Stage

We found no survival rate differences among the three differentiated forms (spindle cell, lymphocytic, epithelial), whereas the rarer undifferentiated tumors carried a poorer prognosis.

Survival by Surgical-Pathological Staging

Our results confirm the validity of Masaoka and associates' classification. Encapsulated thymomas (stage I) have the best prognosis. Thymomas with capsular or pleural invasion (stage II) behave like those invading the adjacent structures (stage III), whereas an intrathoracic dissemination (stage IVa) predicts a bad outcome. The differences are significant ($p < 0.001$) (Fig 2).

Survival by Extent of Resection

When considering the three possibilities of intervention—complete resection, subtotal resection, and biopsy only—

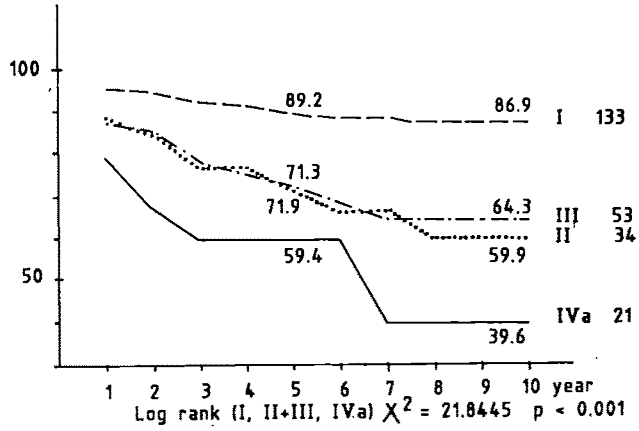


Fig 2. Survival according to surgical-pathological staging.

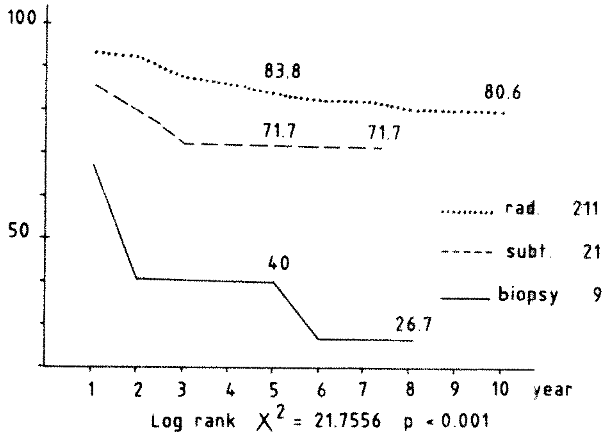


Fig 3. Survival according to the extent of resection (radical, subtotal, biopsy only).

the survival rate curve differences are significant ($p < 0.001$) (Fig 3). It seems worthwhile, therefore, to strive to obtain the most complete resection possible during the removal of a thymoma; nonetheless, patients undergoing subtotal resection still have a survival rate of 70% at 7 years.

Survival by Associated Autoimmune Diseases (Other Than Myasthenia Gravis)

Survival curves from the 15 patients with thymomas in whom pure red cell aplasia, hypogammaglobulinemia, or lupus erythematosus were diagnosed before or after operation indicate that these autoimmune diseases carry a poor prognosis ($p < 0.001$). Their presence is therefore to be regarded as an important negative prognostic factor (Fig 4).

Tumor Recurrence

Tumor recurrence was observed in 14 patients with and 10 patients without MG. The time lapse between operation and the recurrence ranged from 1 to 13 years (mean, 5 years). Ten of the 14 MG patients with relapse had a second operation, 2 were irradiated, and 2 received chemotherapy. Of the 10 patients with tumor relapse without MG, 2 had a second operation, 6 had radiotherapy, and 2 had chemotherapy.

We analyzed tumor recurrence according to the surgical-pathological staging. Encapsulated thymomas (stage I) very rarely recurred (2 of 132 patients, 1.5%); in the present series, only 5 patients with encapsulated thymomas received adjuvant radiotherapy and none had a recurrence.

Invasive thymomas recurred more frequently (22 of 108 patients, 20.4%; stage II, 12.5%; stage III, 29.7%, and stage IVa, 25%). Of the 108 patients with invasive thymoma, 34 had adjuvant therapy (18, radiotherapy; 6, chemotherapy; and 10, both) and 7 had recurrence (20.6%); in these patients, adjuvant therapy was used in 21 radical resections and in 13 subtotal resections, and a reduction in tumor recurrence was observed (3 and 4 recurrences, respectively) as compared with 55 radical and 6 subtotal resections with no adjuvant treatment (11 and 4 recurrences, respectively). Although the numbers are too small to be statistically significant, our results suggest that postoperative radiotherapy and chemotherapy may be useful in these patients, not only after subtotal resection, but after radical resection as well.

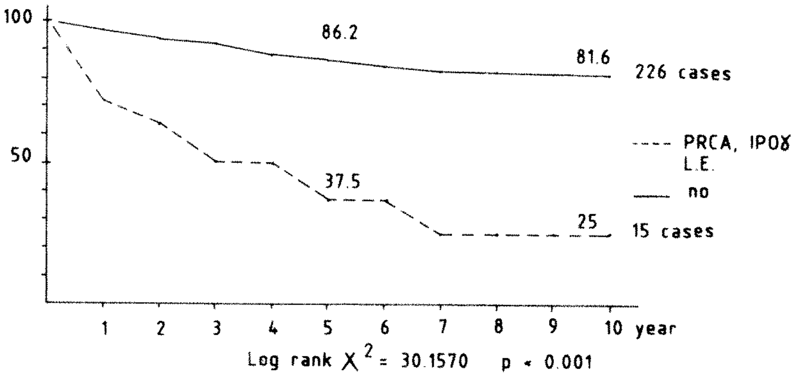
Since 1986 we have started treating patients in stage III and stage IVa with preoperative radiotherapy (30 Gy) when there is clinical evidence of invasiveness. In 3 patients the mass greatly shrank and we could perform a subtotal resection after 3 weeks.

Comment

Thymoma is a histologically well-differentiated tumor in more than 95% of cases, and the carcinomatous variant is rare [9]. Histological classifications based on morphological criteria, such that of Verley and Hollman [9], indicate that spindle cell and predominantly lymphocytic forms are less aggressive than predominantly epithelial forms, but in the present series we found that the difference was not significant.

The classification proposed in 1985 by Marino and Muller-Hermelink [10] into medullary, cortical, and mixed tumors has been adopted by several authors [11, 12] and the results are promising. They demonstrate that medullary thymoma is a somewhat benign disease, whereas cortical thymoma must be considered a malignant tumor, and that a multidisciplinary approach (ie, postoperative radiotherapy in all patients and chemotherapy in select

Fig 4. Survival in patients with pure red cell aplasia (PRCA), hypogammaglobulinemia (Ipoγ), and lupus erythematosus (LE) as compared with the remaining patients with thymoma.



cases) is warranted. Most tumors have a mixed pattern with an intermediate behavior. Studies are in progress at our department to reclassify our series according to this classification.

Macroscopically, in the present series more than 50% of thymomas were encapsulated at the time of operation; prognosis is excellent for these patients and we observed only two recurrences (1.5%). When neoplasm spreads beyond the capsule, the classification of Masaoka and associates based on the extent of tumor invasion is valuable: survival curves show that locally invasive thymomas have a less favorable outcome compared with encapsulated forms. We found no survival rate difference between invasion of perithymic fat and pleura (stage II) and involvement of adjacent lung or pericardium (stage III); conversely, when multiple pleural or pericardial nodes are found (stage IVa), survival rates decrease significantly.

The extent of the resection is another important prognostic factor: in our series radical resection was feasible for all patients in stage I and stage II and for 60% of patients in stage III, but hardly ever for patients in stage IVa; nonetheless, a survival rate of 71% at 7 years was obtained in case of partial resection, while far less survival rates (26% at 8 years) occurred when the tumor was deemed to be unresectable. Thymoma is a low-grade malignancy and our data confirm that a "debulking" operation followed by postoperative radiotherapy achieves high survival rates; some authors [13] reported good results with radiotherapy alone.

In the present study invasive thymomas recurred in 20.4% of the cases: 18% after radical resection and 42% after subtotal resection. Relapses were less frequent when the resection had been followed by radiotherapy or chemotherapy (20.6%) than when it had not (24.6%). This is more evident for subtotal resections, but it has been observed after radical resections as well.

The role of reoperation in the management of recurrence of thymoma has not been clearly defined. In a recent report, Kirschner [14] demonstrated that reoperation is a safe procedure and that the presence of MG has no influence on reintervention: moreover, reoperation is a valid treatment after thymomectomy or incomplete thymectomy. Finally, in cases of initially unresectable tumor treated with adjuvant radiotherapy or chemotherapy, reoperation may be considered as a valid completion of a radical therapy. Our data confirm that survival is better when tumor recurrence was surgically treated than when alternative therapies alone (radiotherapy or chemotherapy) were used, even if the difference was not found to be significant (Fig 5).

There is no general agreement whether radiotherapy should follow the removal of encapsulated thymomas [6]: for these tumors recurrence rarely occurs, and, on the other hand, the risk of pulmonary fibrosis should be kept in mind. Therefore, we think that postoperative radiotherapy should not be routinely performed after removal of encapsulated thymomas. In our series 5 of 133 encapsulated thymomas received postoperative radiotherapy, and only 2 of 127 nonirradiated patients had recurrence: both underwent successful reoperation.

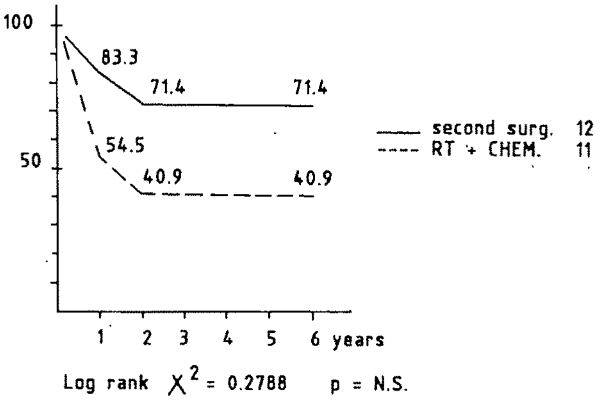


Fig 5. Survival of patients with tumor relapse comparing second operation versus adjuvant therapy alone (RT + CHEM.). (N.S. = *not significant.)*

Prognosis is poor when thymoma is found to be unresectable, or when an association with the autoimmune disorders pure red cell aplasia, hypogammaglobulinemia, or lupus erythematosus is present, as indicated by previous reports [15], but fortunately both these events are rare (3.7% and 4.1%, respectively, in our series).

In the present study, MG was the most frequent cause of death among patients with thymoma and MG, whereas in the group of patients without MG death was most frequently caused by local progression of the neoplasm.

Concerning the effect of MG on survival, our data are in accordance with those of other authors [16, 17], indicating that the presence of MG does not adversely affect the prognosis. Indeed, we found a more favorable prognosis in patients with thymoma and MG, compared with patients who had thymoma without MG ($p < 0.05$). This may be due to either the refinement in techniques for long-term management of patients with MG or the earlier detection of the thymoma, owing to the careful surveillance of the myasthenic patients.

Several conclusions can be drawn from this study: (1) The finding of a mediastinal mass in a patient with MG is highly suggestive of thymoma. If the patient has no MG, we think that a preoperative diagnosis should be established because the treatment will be different according to the histological results. We generally use a parasternal mediastinotomy, with removal of the second costal cartilage.

(2) Subtotal resection of invasive thymomas may yield surprisingly high survival rates, particularly if followed by postoperative radiotherapy. Our results demonstrate that partial resection is effective, and we think that the surgeon must strive to remove most of the tumor, even if some tumor fragments will be left behind.

(3) Controversy persists over the optimal surgical approach for patients with thymoma. Our standard surgical approach is a median longitudinal sternotomy and complete resection of the thymus and perithymic fat from the sternal notch down to the pericardium. We think that this

access permits a thorough view of the great vessels, not limiting a possible exposure of the pleural space. No major complications occurred with this procedure; a focus of sternal osteomyelitis developed in 1 patient and eventually healed after the removal of a sternal stitch a few months after the operation.

(4) The first line of therapy for thymoma is operation: radiotherapy or chemotherapy, alone or together, can yield long-term survival, but hardly ever complete remission. Neoadjuvant radiotherapy or chemotherapy, if clinical evidence of invasiveness exists, permits easier tumor excision; adjuvant therapies are indicated for all patients with invasive thymoma, regardless of the extent of the resection.

With such a multidisciplinary approach, in the present series 86.9% of the patients with encapsulated thymoma, 62% with local invasion, and 40% with pleural metastatic seeding are alive up to 10 years. These results are extremely impressive for a potentially malignant and invasive neoplasm.

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Empyema and Bronchopleural Fistula

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CORRESPONDENCE

Double Outlet Left Ventricle—Long Survival After Surgical Correction

To the Editor:

In 1974, one of the earliest intracardiac repairs of double outlet left ventricle was performed by one of us (D.G.M.) and published in *The Annals* [1]. Surgical treatment of double-outlet left ventricle had previously been achieved in only a few patients [2, 3], but without reports of long-term follow-up. We wish to place on record successful revision of our original repair 16 years after operation at age 12 years. The patient is now 28 years of age.

The malformation under consideration is the converse of double-outlet right ventricle, ie, in the former both great arteries arise entirely or predominantly from the morphologic left ventricle. Double-outlet left ventricle is among the rarest of abnormal ventriculoarterial alignments [4–6]. A ventricular septal defect provides the morphologic right ventricle with its only exit. Pulmonic stenosis can coexist.

Our patient was cyanotic at birth and was catheterized at ages 3 months and 7 years with inconclusive results. A presumptive diagnosis of tetralogy of Fallot led to a Waterston shunt. When the patient was aged 12 years, the correct diagnosis of double-outlet left ventricle, ventricular septal defect, and pulmonic stenosis was made at open operation. The bicuspid stenotic pulmonic valve was oversewn, the Waterston shunt was revised, the ventricular septal defect was closed, and a 20-mm woven Dacron nonvalved conduit was inserted between the right ventricle and pulmonary trunk. Two months after discharge, the patient resumed nearly full activity. He was lost to follow-up until 1987 when he returned to the UCLA Medical Center with a history of seizure activity and moderate cyanosis. Computed tomographic scan and magnetic resonance images revealed an old cerebral abscess. Two-dimensional echocardiography, cardiac catheterization, and angiography disclosed an enlarged hypertrophied right ventricle with an incisional aneurysm from the apex to the origin of the conduit, which was obstructed in its midportion. Right ventricular systolic pressure was systemic (144/6 to 10 mm Hg) and pulmonary arterial pressure was 16/10 mm Hg. There was a small bidirectional shunt across the ventricular septal defect patch. Modest flow from the left ventricle into the pulmonary trunk indicated that the pulmonic valve had not been completely sealed.

At reoperation (Fig 1), the right ventricular aneurysm was resected and the nonvalved conduit was replaced with a right ventricle-to-pulmonary artery 24-mm aortic homograft with right ventricular extension of albumin-treated Dacron. The residual ventricular septal defect leak was repaired, an anomalous right superior pulmonary vein was incorporated into the left atrium during closure of a midportion atrial septal defect, and a small patent ductus arteriosus was divided.

The postoperative course was uneventful except for echocardiographic evidence of a mobile clot in the apex of the left ventricle requiring anticoagulation for several months. The pa-

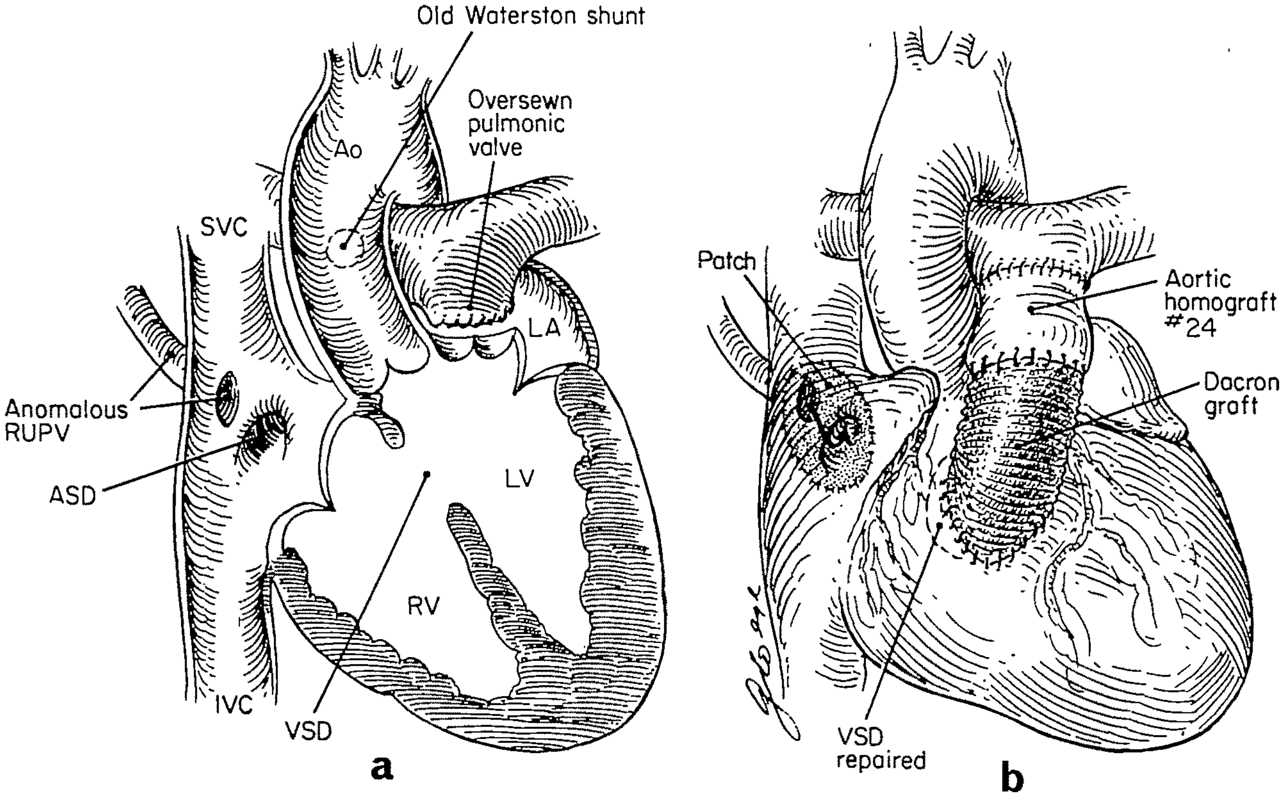

Fig 1. (a) Morphologic findings before revision. The aorta (Ao) *and pulmonary artery were entirely committed to the left ventricle* (LV). *The site of the old Waterston shunt was identified. The pulmonic valve was oversewn. A small leak was present across the ventricular septal defect* (VSD) *patch (removed in this figure). There was an anomalous right upper pulmonary vein* (RUPV) *and a midportion atrial septal defect* (ASD). *The large right ventricular incisional aneurysm is not shown. (b) Reoperation consisted of resection of the right ventricular aneurysm, repair of the VSD patch leak, and replacement of the nonvalved conduit with a right ventricle-to-pulmonary artery 24-mm aortic homograft with right ventricular extension of albumin-treated Dacron. The anomalous RUPV was incorporated into the left atrium (LA) during repair of the ASD. A small patent ductus (not shown) was divided.*

tient slowly resumed full activities. At his 18-month postoperative visit, he was gainfully employed.

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Mitral Valve Reoperation

To the Editor:

Praeger and co-workers [1] are to be commended for bringing to our attention once again the benefits of thoracotomy for reoperations on the mitral valve. I share their enthusiasm for this approach, and have used it for mitral operations in patients with patent coronary bypass grafts, for tricuspid operations in patients who have previously undergone mitral valve operations, and in some patients who have never had cardiac operations but have relative contraindications to median sternotomy, such as previous irradiation in conjunction with mastectomy or previous full-thickness burns of the anterior chest wall.

Dr Praeger and co-workers emphasize the safety of spontaneous hypothermic ventricular fibrillation during the performance of mitral valve operations by this approach. As an advocate of noncardioplegic coronary bypass [2], I certainly support their assertion. However, I would like to question the wisdom of their insistence on retrograde pulsatile cardiopulmonary bypass to enhance myocardial perfusion in these patients. Because the operative technique they describe involves femoral artery cannulation for arterial return, there are two reasons to forego pulsatile cardiopulmonary bypass in such patients.

First, the transmission of pulsatile waves to the coronary arteries is substantially reduced when arterial inflow is provided remotely through a relatively small bore cannula at the femoral artery. More importantly, retrograde pulsatile flow can only increase the already notable risk of retrograde dissection associated with femoral artery cannulation. Because atherosclerotic plaques in the aorta are laid down in the direction of antegrade blood flow, they are more susceptible to detachment by retrograde flow. It seems unnecessarily hazardous to subject these plaques to the high-velocity jet that inevitably accompanies pulsatile flow through a small cannula (the so-called sandblast effect). The patients requiring reoperative mitral valve procedures are often small, older women in whom large cannulas cannot be inserted into the femoral artery. It is usually feasible to cannulate the greater curvature of the ascending aorta through a right thoracotomy in such patients and to insert a thin-wall, high-flow cannula suitable for antegrade pulsatile flow. If aortic cannulation is not feasible, we prefer nonpulsatile retrograde flow. Retrograde pulsatile flow in these patients appears to pose a real risk for a theoretical gain, always a poor bargain.

With this one note of caution, however, I enthusiastically support the approach of Dr Praeger and his co-workers.

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Early Restenosis After Extended End-to-End Anastomosis at Neonatal Age

To the Editor:

In the May 1990 issue of *The Annals* Maehara, de Leval, and Elliott [1] present a neonate in whom unusually early restenosis developed after radical end-to-end repair of a preductal subtype of aortic coarctation and hypoplasia of the aortic arch. Although we think that the surgical management of coarctation of the aorta and hypoplasia of the aortic arch as first described by Zannini and associates [2] and later perfected by Elliott [3] is an appropriate technique for this combination of aortic arch anomalies, we believe that the described technique fails to emphasize the importance of complete resection of the isthmus.

It is known from histologic studies that the distribution of ductal tissue in aortic coarctation may be at both sides of the diaphragmatic ridge [4, 5]. We confirmed that in the paraductal subtype of coarctation, being the result of having received part of its flow in embryonic and fetal life in a retrograde fashion from the ductus arteriosus, ductal tissue may be found at both the downstream (facing the descending aorta) and the upstream (facing the aortic arch) sides of the ridge. In the preductal subtype, however, it is almost always confined to the downstream side of the ridge [6].

However, as one can never be absolutely sure about the extent of ductal tissue proximal to the ductal-isthmic junction, it is of paramount importance to completely resect both the coarctation and the isthmus, not only in the paraductal but also in the preductal subtype of coarctation (Figs 1–3). Using this approach virtually all ductal tissue is removed. Subsequently, depending on the proximal extent and severity of the aortic arch hypoplasia, the techniques as described by Amato and co-workers [7] or Vincent and associates [8] to enlarge the diameter of the distal transverse arch can be applied, or the incision on the undersurface of the aortic arch can be continued further proximal to enlarge the diameter of the complete transverse arch, as described by Elliott.

Based on the aforementioned considerations, we think that, as far as apparent from the presented figures in Elliott's and Maehara's reports [1, 3], the resection of the isthmus in the

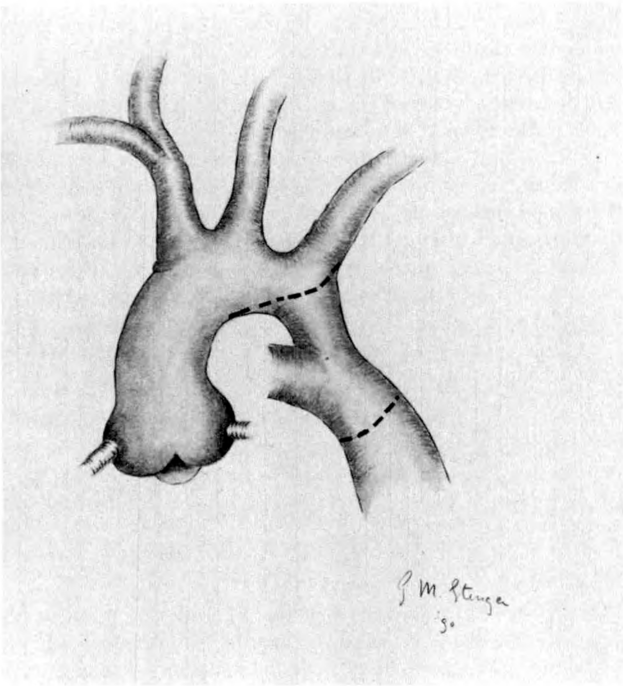

Fig 1. Incision lines in the transverse aortic arch and the upper descending aorta in coarctation of the aorta and moderate hypoplasia of the distal transverse aortic arch.

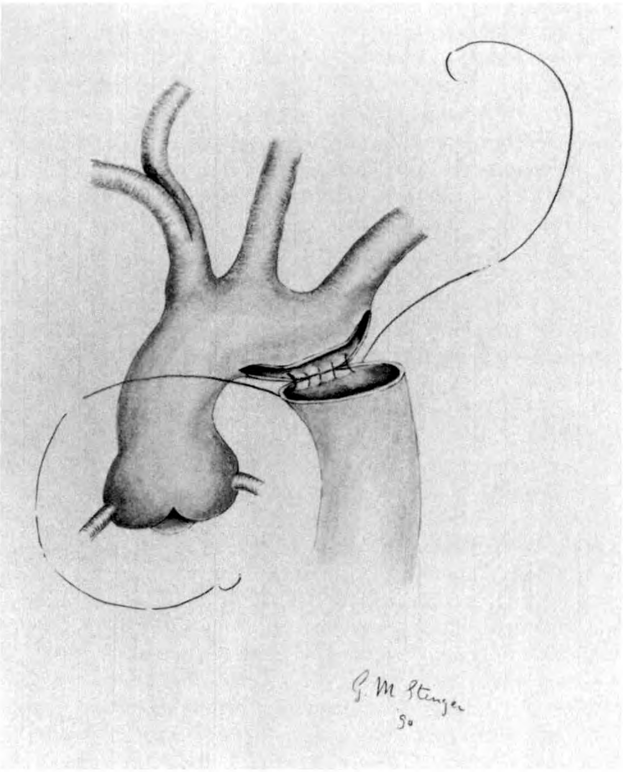

Fig 2. The resection is extended just distal to the origin of the left subclavian artery and the undersurface of the aortic arch is incised in a cephalad direction to achieve a maximally wide anastomotic diameter. The descending aorta is transected obliquely.

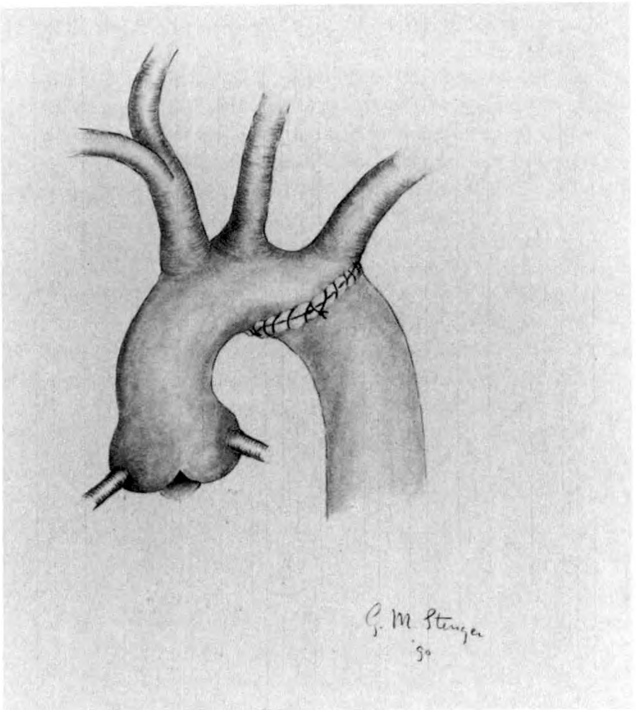

Fig 3. A matching end-to-end anastomosis is created.

presented neonate may have been insufficient. Hence, ductal tissue at the proximal suture line may have continued to exert its coarctogenetic potential. Based on the thorough histologic study of Elzenga and Gittenberger-de Groot [5] and our own histologic research, it seems to be unlikely, as Maehara and associates suggest, that in the presented neonate ductal tissue was probably present at the inferior surface of the aortic arch. Such a finding would not be in concordance with our hypothesis of the ontogenesis of coarctation of the aorta and the deductive hypothesis of the distribution of ductal tissue [9].

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Leon K. Lacquet, MD

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of the aorta. An age dependent spectrum. Br Heart J 1983;49:317–23.
6. Van Son JAM, Daniëls O, Vincent JG, van Lier HJJ, Lacquet LK. Appraisal of resection and end-to-end anastomosis for repair of coarctation of the aorta in infancy: preference for resection. Ann Thorac Surg 1989;48:496–502.
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Reply

To the Editor:

Thank you very much for the opportunity to reply to the letter of Drs van Son, Smedts, and Lacquet. I am delighted to acknowledge their contribution to this field and am aware of their description of ductal tissue distribution. Over the last 5 years we have taken a more conservative view of tissue resection in the arch, preferring to use visually normal tissue to create a long anastomosis. In our experience, the reported case is the only one of early restenosis after such extended end-to-end repair. The detailed results of a large series of patients will be published shortly.

Thus, although we accept the possibility that inadequate resection of ductal tissue might have been a factor (indeed, we pointed this out in the paper in our case report), we believe that a long anastomosis may be equally effective in preventing the likelihood of recurrence and avoids the complexities of the techniques described by Amato or Vincent. Clearly the only way to differentiate between these two techniques is to organize and carry out a prospective, randomized trial of the two methods. As the extended end-to-end repair gains acceptance this may be a valid proposal.

Martin J. Elliott, MD, FRCS

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Metallic Surgical Clips and Magnetic Resonance Imaging

To the Editor:

Gold and associates [1] discuss the nonmigration of two types of surgical clips in response to a high-intensity diagnostic magnetic resonance imaging (MRI) field. Other than metallic or ferromagnetic the authors do not identify the composition of the tested clips. The use of these words is insufficiently precise to predict the behavior of surgical appliances in a strong magnetic field.

It is known that clips containing elements with magnetic properties show motion in response to an MRI field [2]. There are five elements on the periodic table that display magnetic properties. These elements are iron, cobalt, nickel, gadolinium, and dysprosium [3].

Iron is familiar in our everyday experience. Canadian five-cent pieces have a high content of nickel and are magnetic. Cobalt is magnetic, and a stable isotope of cobalt is very radioactive and thus can be a dangerous component of archaic radiotherapy generators. Gadolinium and dysprosium are rare-earth elements occurring in the lanthanide series of the periodic table. Gadolinium is used as contrast material in MRI applications. Gold is noble, precious, and nonmagnetic [4].

A biomedical alloy composed of any magnetic element would be expected to react in an imposed magnetic field. Those without these elements would not. Thus, surgical clips composed of titanium only would not be expected to react to an MRI field.

Further investigations should identify the precise nature of the alloy of these surgical devices. With this information it could be predicted which products will be safe in the use of MRI.

Any surgical appliance containing an alloy of iron, cobalt, nickel, gadolinium, or dysprosium should be carefully defined and properly interpreted before MRI examination.

Fred Weber, MD

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Reply

To the Editor:

My colleagues and I would like to thank Dr Weber for his comments concerning the implantation of metallic clips and their relative safety in patients undergoing high-field-strength magnetic resonance imaging. As Dr Weber will note, the specific clips tested are identified as USSC Auto Suture Titanium, model No. 132861, manufactured by United States Surgical, and Weck Tantalum Hemiclip model No. 523100, manufactured by the Weck Corporation. These clips are manufactured of two different materials demonstrated not to have magnetic properties as described.

Titanium, tantalum, and stainless steel are the most commonly employed materials for surgical clip manufacture. The former two are elemental materials that have no activity in magnetic fields; the latter is a ferrous alloy that will have a certain amount of magnetic activity. The magnetic moment-arm of any alloy containing materials with magnetic properties can be precisely determined. Although magnetic clips can be manufactured of materials that are intrinsically nonmagnetic, there are potential advantages of alloys containing magnetic materials for other surgically implanted devices or prostheses. The knowledge of the precise response in a high-energy magnetic field and a means for predicting the magnetic moment-arm before subjecting the patient and the prosthesis to the magnetic imaging device would be highly advantageous. Clearly, it is the composition of the material, the mass of the device, and the orientation of the device to the magnetic field axis that will determine the potential for dislodgment and migration.

We certainly agree that any surgical device that contains an alloy of iron, cobalt, nickel, gadolinium, or dysprosium should be carefully evaluated before subjecting the recipient of such implant to a high-field-strength magnetic resonance scan. We appreciate the comments of Dr Weber and his discussion of this important topic.

Jeffrey P. Gold, MD

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Esophagogastrectomy via Left Thoracotomy

To the Editor:

My colleagues and I read with interest the paper by Page and associates [1] entitled "Esophagogastrectomy via left thoracophrenotomy." We congratulate Page and associates on their good results. However, they state "Although this approach [the left thoracophrenotomy] is still practiced by some thoracic surgeons on both sides of the Atlantic, little appears in the literature about this technique." May I draw your attention to the fact that this technique was described and published in 1983 in the *Annals of Surgery* [2], where it was stated "In the latter part of the series [ie, in 23 patients], all lesions, irrespective of their location, were approached through the left chest. This approach is easy and adequate to provide access both to the esophagus and to the stomach. Second, it has less postoperative respiratory complications compared with a two-stage procedure. Third, if the tumor is behind the aortic arch, the aorta can be mobilized easily, and anastomosis with the help of the stapler can be achieved either below, above, or lateral to the arch. Finally, if the lesion is unresectable, a Celestin tube can be placed in position through the same incision."

R. Behl, MS, FRCS(Eng)

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References

1. Page RD, Khalil JF, Whyte RI, Kaplan DK, Donnelly RJ. Esophagogastrectomy via left thoracotomy. Ann Thorac Surg 1990;49:763–6.

Reply

To the Editor:

I am pleased to respond to the letter of Mr Behl in which he refers to our paper reporting 115 patients who underwent esophagogastrectomy for malignant disease through a left thoracotomy incision. We were aware of the paper by Behl and his colleagues and, indeed, referred to this in our previous paper, published in *Thorax* [1]. Others have also reported results of this technique, and we did not make any claims to originality. The purpose in presenting our results for publication was to draw attention again to the technique at a time when most reports refer to the transhiatal, thoracoabdominal, or Ivor Lewis approaches to esophageal resection.

The left thoracotomy approach was first described in the early days of esophageal surgery, and I would entirely agree with Mr Behl regarding its advantages. It is true, however, that only occasional reports of the technique appear in the surgical literature these days, and I hope that our contribution will help, with others, to maintain the position of the operation in modern thoracic surgery.

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Reference

1. Donnelly RJ, Sastry MR, Wright CD. Oesophagogastrectomy using the end to end anastomotic stapler: results of the first 100 patients. Thorax 1985;40:958–9.

Symposium on Thoracic Surgical Oncology

To the Editor:

I would like to bring to the attention of *The Annals* an error of omission in the Symposium of Thoracic Surgical Oncology [1]. Due to editorial constraints two important members of the Surgery Branch who made valuable contributions before the Thoracic Oncology Section was established were omitted. These include Dr M. Wayne Flye and Dr Michael R. Johnston. These thoracic surgeons were in the Surgery Branch as Senior Investigators between 1977 and 1982. During that interval it was recognized that the volume of thoracic surgery at the National Cancer Institute demanded the establishment of a Thoracic Oncology Section which Dr Roth, indeed, established in 1981. I felt it was important to bring this to your attention, particularly because both these gentlemen have established themselves not only as technically superb surgeons but also as innovators in the field of thoracic oncology.

Harvey I. Pass, MD

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Reference

1. Symposium on Thoracic Surgical Oncology [Report]. Ann Thorac Surg 1990;50:500–7.

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1990 Interim Meeting
The Society of Thoracic Surgeons

The Interim Meeting of The Society of Thoracic Surgeons was held at the Hyatt Regency Hotel, Chicago, Illinois, September 21–23, 1990. Among the total attendance of 1,367 for this weekend meeting were 467 members and 214 guests who attended the meeting program and 169 spouses and 517 exhibitors who participated in the weekend events. Praise from those attending underscored the value of scheduling this special meeting to bridge the 20-month interval between annual meetings caused by the change from September to a February schedule.

The Interim Meeting format was planned to provide equal time to presentations on social and economic issues and on scientific topics. The Friday afternoon Medico-Legal Session led off with a review of current issues affecting our profession. Next was a minisymposium entitled Health Care in America in which prominent lay experts discussed the major forces that are changing American medicine.

Saturday morning began with a Workshop on Nomenclature and Coding with special emphasis on the reimbursement process. The morning plenary session was devoted to the topic of Physician Reimbursement. The substantial efforts of the Society were highlighted by a presentation of the results of the resurvey of the profession by Abt Associates.

A special luncheon address was delivered by Dr Louis W. Sullivan, Secretary of the Department of Health and Human Services. Dr Sullivan spoke on physician payment reform as it relates to controlling health care costs in America and to allocation of resources to meet ongoing health care needs. His comments were warmly received by the members and guests.

An outstanding Scientific Program occupied Saturday afternoon and Sunday morning. Special parallel sessions on general thoracic and adult and pediatric cardiac surgery focused both the presentations and discussions and heightened the interest of those working in these areas. Sunday's session was preceded with a presentation of the initial results of the STS National Database and an introduction to the software. After some excellent presentations of topics of general interest during the Sunday morning plenary session, parallel "How to Do It" sessions were conducted in the three special interest areas.

As Program Chairman, I am indebted to the Ad Hoc Committee on the Interim Meeting for selecting topics and arranging speakers. In particular, credit for the success of the Scientific Sessions belongs to Dr Robert Guyton and to Drs John Brown and Peter Pairolero who ably assisted him. Dr George Miller organized the excellent Reimbursement Session and Dr Thomas Bartley produced the stimulating Medico-Legal Session. The well-attended workshops on Nomenclature and Coding and on the STS National Database were constructed by Dr Sidney Levitsky and Dr Richard Clark, respectively. President Gerald Rainer offered much support and useful advice and, as usual, the Society staff did a fine job with hotel and meeting arrangements and a myriad of details.

February Meeting in San Francisco

The Twenty-seventh Annual Meeting of The Society of Thoracic Surgeons will be held at the Moscone Center, San Francisco, on February 18–20, 1991. The Program Committee has received over 300 abstracts and their high quality ensures pertinent and interesting presentations in all areas of interest. Dr Daniel Ullyot and his Local Arrangements Committee have prepared a special welcome to the "City by the Bay," and Mrs Bobby Jamplis has organized many interesting activities for spouses. Please be sure to mark your calendars and make the necessary arrangements to attend what promises to be an outstanding meeting.

Richard P. Anderson, MD
Secretary

THE SOCIETY OF THORACIC SURGEONS

Twenty-seventh Annual Meeting
February 18–20, 1991
Moscone Center, San Francisco, California

The Twenty-seventh Annual Meeting of The Society of Thoracic Surgeons will be held at the Moscone Center on February 18–20, 1991, preceded by the Twenty-fourth Postgraduate Program on Sunday, February 17. The meeting is open to all duly qualified physicians. Both members and nonmembers are urged to register in advance.

The 1990 Program Committee is very pleased with the response to the abstract call, counting 306 abstracts submitted. In addition to the quantity, the high quality of the abstracts made possible the development of a program that represents all aspects of adult and pediatric cardiac surgery and general thoracic surgery. The utilization of breakout sessions introduced very successfully at the last Annual Meeting is being expanded. On Sunday afternoon, immediately following the Postgraduate Program, there will be an important session entitled "STS National Database—A Significant Tool for Clinical Practice." On Monday afternoon, there will be parallel sessions entitled "General Thoracic I," "Heart Transplant Research," and "Adult Cardiac I," running simultaneously from 1:30 to 2:45.

On Tuesday afternoon, all sessions will run from 1:30 to 5:00 PM. Session I will include General Thoracic II, followed by Lung Transplant Research. Session II will include Cardiac Research, followed by Electrophysiology and Cardiac Research, and Session III includes Adult Cardiac II, followed by Congenital Cardiac.

The popular Tuesday morning Problem Case Presentations and the Wednesday morning Clinical Workshops will continue. In addition, on both Tuesday and Wednesday there will be small group sessions on CPT Nomenclature and the coding process.

The Committee had a significant increase in the number of video tapes submitted for the Annual Movie Night, making it possible to develop an excellent program representative of all aspects of the specialty. The movie night session will be in the Hilton Hotel.

At 11:15 AM on Tuesday, Harry Schwartz, PhD, columnist for *American Medical News*, will present the first Ralph D. Alley Lecture entitled, "The Future of American Thoracic Surgery."

Registration and Fees

An advance registration form with hotel reservation information and details regarding spouses' activities will be mailed to Society members. Nonmembers should write to the Secretary, Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611.

Members are not required to pay a registration fee for the Scientific Program. Residents and fellows may register without payment of a registration fee upon presentation of a letter from their chief of service. The fee for other physicians is $250, except guest speakers, authors, coauthors, and invited discussants. Nurses and paramedical personnel may register upon payment of a $40 fee and presentation of a letter of introduction from a Society member.

The Postgraduate Program is sponsored by the Committee on Postgraduate Education of The Society. Registration fee, which includes lunch, for the Postgraduate Program is $65 for all physicians, residents, and fellows.

There will be no advance registration for the concurrent Problem Case Presentations on Tuesday, February 19, or the Clinical Workshops on Wednesday, February 20. Attendance will be by ticket only, and each seminar is limited to 35 physicians. Tickets can be purchased at the Society's registration desk on Monday, February 18, starting at 12:30 PM. A continental breakfast is included.

Presentation and Publication

Papers presented at the Scientific Session must be submitted to the Secretary at the time of presentation, or may be submitted to the Editor prior to the meeting for possible earlier publication.

Speakers for the Scientific Sessions should limit their presentations to 10 minutes. They are requested to meet with the projectionist in the preview room prior to the opening of their session to prepare their slides for presentation.

Those who wish to discuss a paper may write the Secretary prior to the meeting. Discussants from the floor should submit their names to the Moderator at the podium prior to the opening of the session during which the paper is to be presented. Discussants from the floor are limited to 2 minutes; primary discussants are limited to 3 minutes.

Discussants will receive a copy of their remarks shortly after the Annual Meeting. Any delay in the return of the corrected discussion to the Editor will hold up publication of the paper. Timely response of all authors and discussants is, therefore, urged since delays are unfair to those who promptly return their material for publication.

Accreditation

The Society of Thoracic Surgeons is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. One credit hour in Category I of the Physician's Recognition Award of the American Medical Association may be claimed for each hour of participation by the individual physician. The Postgraduate Program is authorized for eight hours of Category I CME credit.

TWENTY-FOURTH POSTGRADUATE PROGRAM
THE SOCIETY OF THORACIC SURGEONS

Sunday, February 17, 1991
Moscone Center, San Francisco, California

8:00–12:00 **Morning Session**

8:00 Introduction to the 1991 Postgraduate Course
Andrew S. Wechsler, Richmond, VA, Co-Chairman, Postgraduate Committee

I. Mini Symposium: Advanced Cardiac Valve Surgery
Moderator: Andrew S. Wechsler, Richmond, VA

8:10 Myocardial Protection for Complex Valve and Valve-Coronary Grafting Procedures
Nicholas T. Kouchoukos, St. Louis, MO

8:30 Allograft Aortic Valve and Aortic Root Replacement
Donald B. Doty, Salt Lake City, UT

8:50 The Densely Calcified Mitral Valve and Annulus
Noel L. Mills, New Orleans, LA

9:10 Aortic Valve Replacement With Major Aortic Valve and Aortic Root Calcification
John B. Flege, Jr, Cincinnati, OH

9:30 Tricuspid Regurgitation: Assessment and Intraoperative Management
Lawrence H. Cohn, Boston, MA

9:50 Repeat Operations for Cardiac Valve Disease—Tricks of the Trade
D. Craig Miller, Stanford, CA

11:00 **II. C.C.C.E.T.S. Basic Science Lecture***
Introduction
George C. Kaiser, St. Louis, MO, Chairman, Coordinating Committee for Continuing Education in Thoracic Surgery

Vascular Regulation by Mediators From the Endothelium
Professor Sir John Vane, FRS,** The William Harvey Research Institute, St. Bartholomew's Hospital Medical School, London, England

12:00–1:30 Luncheon

Luncheon Address: Future Directions in Cardiovascular Health Care
Jack M. Matloff, Los Angeles, CA

1:30–5:00 **Afternoon Session**

Introduction
Kent W. Jones, Salt Lake City, UT, Co-Chairman, Postgraduate Committee

III. Mini Symposium: Treatment of Congenital Pulmonary Disorders
Moderator: Kent W. Jones, Salt Lake City, UT

1:30 Tracheoesophageal Fistula
Darroch W. O. Moores, Albany, NY

1:50 Bronchopulmonary Foregut Malformations
Larry R. Kaiser,** St. Louis, MO

2:10 Congenital Tracheal Stenosis
Robert M. Filler,** Toronto, Ont, Canada

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* Open Session

** By Invitation

2:30 Lobar Emphysema and Cystic Adenomatoid Malformation
J. Alex Haller, Jr,** Baltimore, MD

2:50 Panel Discussion: Questions and Answers

IV. State of the Art Lectures
Moderator: Kent W. Jones, Salt Lake City, UT

3:45 Bronchoplastic Techniques
Jean Deslauriers, Ste-Foy, Que, Canada

4:05 Surgical Treatment of Esophageal Motility Disorders
David J. Sugarbaker,** Boston, MA

4:25 Automatic Internal Converter-Defibrillators
Ralph J. Damiano,** Richmond, VA

4:45 Panel Discussion: Questions and Answers

5:10–6:15 **STS National Database**

A Significant Tool for Clinical Practice
Richard E. Clark, Pittsburgh, PA

PROGRAM
TWENTY-SEVENTH ANNUAL MEETING
THE SOCIETY OF THORACIC SURGEONS

February 18–20, 1991

February 18, 1991 (Monday)
Morning

8:00 Business Meeting (members only)

8:05 Welcome

8:15–11:15 **Scientific Session**

1. **J. Maxwell Chamberlain Memorial Paper**

   The Role of Staging in Prognosis and Management of Thymoma
   Earle W. Wilkins, Hermes C. Grillo, J. Gordon Scannell, Ashby C. Moncure, and Douglas J. Mathisen, Boston, MA

2. Sequential Bilateral Lung Transplantation: Results From 16 Consecutive Patients
   Larry R. Kaiser, Michael K. Pasque, Carolyn M. Dresler, Elbert P. Trulock, Anastasios Triantafillou, and Joel D. Cooper, St. Louis, MO

3. Staged Repair of Diffuse Aneurysm of Aorta Using "Elephant Trunk" Principle for Ascending and Arch Replacement
   E. Stanley Crawford, Lars G. Svensson, Joseph S. Coselli, Kenneth R. Hess, Hazim J. Safi, and Frederick A. Meadors, Houston, TX

4. Inferior Epigastric Artery as a Coronary Conduit
   Hendrick B. Barner, Keith S. Naunheim, Andrew C. Fiore, and Howard H. Harris, St. Louis, MO

5. Surgery of Fulminant Pulmonary Embolism: Indication, Diagnostics, Technique, and Results
   C. Schmid, S. Zietlo, T. O. F. Wagner, J. Laas, and H. G. Borst, Hannover, Germany

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** By Invitation

6. Results of Fontan Operation for Univentricular Heart
Amram Cohen, John Dyck, Dolores Poppe, Jeffrey Smallhorn, Robert Freedom, George Trusler, John Coles, Fred Moes, Ivan Rebeyka, and William Williams, Washington, DC

7. Indications and Limits of Aortic Valve Reconstruction
Carlos G. Duran, Naresh Kumar, Begonia Gometza, and Zohair Al Halees, Riyadh, Saudi Arabia

11:15–12 Noon **Presidential Address**
W. Gerald Rainer

Afternoon

1:30–5:00 **Parallel Scientific Sessions**
Session I

1:30–2:45 **General Thoracic I**
Moderator: Douglas J. Mathisen, Boston, MA

8. Main Bronchial Sleeve Resection With Pulmonary Conservation
Joseph R. Newton, Jr, Hermes C. Grillo, and Douglas J. Mathisen, Boston, MA

9. TNM Staging and Long-Term Follow-up After Sleeve Resection for Bronchogenic Carcinoma
P. Van Schil, A. Brutel de la Riviere, P. Knaepen, H. van Swieten, J. Defauw, and J. van den Bosch, Nieuwegein, Netherlands

10. Bronchopleural Fistula After Stapled Closure of the Bronchus
S. Russell Vester, L. Penfield Faber, C. Frederick Kittle, William H. Warren, and Robert J. Jensik, Chicago, IL

11. Multiple Primary Lung Carcinomas: Treatment and Prognosis
Todd K. Rosengart, Nael Martini, Pierre Ghosn, and Michael E. Burt, New York, NY

12. CUSA (Cavitron Ultrasonic Suctioning Aspirator) for Lung Resection
Gary T. Verazin, Anne-Marie Regal, Joseph G. Antkowiak, Zafar Parvez, and Hiroshi Takita, Buffalo, NY

Session II

1:30–2:45 **Heart Transplant Research**
Moderator: R. Morton Bolman III, Minneapolis, MN

13. Noninvasive Detection of Experimental Heart Transplant Rejection With Positron Emission Tomography
Steven J. Hoff, James R. Stewart, William H. Frist, Robert Kessler, Martin Sandler, James B. Atkinson, John A. Carey, and Walter H. Merrill, Nashville, TN

14. Weight Is Not an Accurate Criterion for Adult Cardiac Transplant Size Matching
Barry B. K. Chan, Kirk J. Fleischer, V. Colt Peyton, Terry L. Flanagan, Curtis G. Tribble, James Bergin, Robert S. Gibson, and Irving L. Kron, Charlottesville, VA

15. UW Solution for Human Donor Heart Preservation: Initial Clinical Experience
Valluvan Jeevanandam, Mark L. Barr, Gary Y. Ott, Juan A. Sanchez, Charles C. Marboe, Joseph S. Auteri, Craig R. Smith, and Eric A. Rose, New York, NY

16. Triiodothyronine Enhances Left Ventricular Performance in Injured, but Not Normal Hearts
Cornelius M. Dyke, Thomas Yeh, Jr, Jon Lehman, Rebecca Dignan, Mai Ding, Anwar S. Abd-Elfattah, Andrew S. Wechsler, and David Salter, Richmond, VA

17. First Successful Bridge to Cardiac Transplantation Using Direct Mechanical Ventricular Actuation
James E. Lowe, Mark P. Anstadt, Peter Van Tright, Peter K. Smith, Paul J. Hendry, Mark D. Plunkett, and George L. Anstadt, Durham, NC

Session III

1:30–2:45 **Adult Cardiac I**
Moderator: Alexander S. Geha, Cleveland, OH

18. The Right Gastroepiploic Artery as a Coronary Artery Bypass Graft
John Pym, John O. Parker, and Roxroy O. West, Kingston, Ont, Canada

19. Multiple Reoperative Coronary Artery Bypass Surgery
Kevin D. Accola, Joseph M. Craver, Ellis L. Jones, William S. Weintraub, and Robert A. Guyton, Atlanta, GA

20. Synchronous Surgical Treatment of Ischemic Heart and Cerebrovascular Obstructive Disease. Long-Term Follow-up
Freddy Vermeulen, Ruben Hamerlijnck, Jo Defauw, and Sjef Ernst, Nieuwegein, Netherlands

21. Extracorporeal Circulation, Profound Hypothermia, and Circulatory Arrest for Otherwise Inoperable Intracranial Tumors
Mark D. Williams, W. Gerald Rainer, Henry Fieger, and Mary Sanchez, Denver, CO

22. Early Experience With Adult ECMO in the Modern Era
Harry L. Anderson III, Ralph E. Delius, James M. Sinard, Ken R. McCurry, Charles J. Shanley, Robin A. Chapman, Michael B. Shapiro, Jorge L. Rodriguez, and Robert H. Bartlett, Ann Arbor, MI

3:30–5:00 Business Meeting (members only)

Evening

8:00–10:00 **Surgical Motion Pictures**
Moderators: Alexander S. Geha, Cleveland, OH, and Robert A. Guyton, Atlanta, GA

1. Spiral Vein Graft for Superior Vena Cava Syndrome
George B. Haasler, Milwaukee, WI

2. Transcervical-Transsternal Maximal Thymectomy for Myasthenia Gravis
Alfred Jaretzki III, New York, NY

3. Correction of Postpneumonectomy Mediastinal Overshift by Insertion of Silastic Tissue Expander
Frederick L. Grover, J. Martin Smith, John H. Calhoon, William C. Hall, Deborah K. Rasch, Bruce M. Schnapf, David Cohen, Donald Campbell, and J. Kent Trinkle, San Antonio, TX

4. Aortic Valve Replacement With Pulmonary Autotransplant and Pulmonary Homograft Replacement for Rheumatic Aortic Insufficiency With Previous Mitral Repair in a 17-Year-Old Girl
Stephen B. Colvin, Frank C. Spencer, Aubrey Galloway, and Alan Katz, New York, NY

5. Warm Heart Surgery for Coronary Artery Bypass
Samuel V. Lichtenstein and Tomas A. Salerno, Toronto, Ont, Canada

6. Carinal Resection
Tsuguo Naruke, Tokyo, Japan

7. Perinatal Management of Massive Left Ventricular Rhabdomyoma
Harold D. Head, Kenneth L. Jue, and James V. Prochazka, Dayton, OH

8. Surgical Treatment of Infected Coarctation Graft and Aortobronchial Fistula
Michael J. DaValle, Chicago, IL

9. Thoracoscopic Management of a Recurrent Spontaneous Pneumothorax
J. K. Champion, Cleveland, TN

February 19, 1991 (Tuesday)
Morning

7:00–8:00 **Breakfast Sessions**
No advance registration. Attendance by ticket only and limited to 35 per seminar. Tickets can be purchased at registration desk on Monday, February 18, starting at 12:30 PM. Price of ticket covers attendance at seminar and continental breakfast. These sessions run concurrently.

CPT Nomenclature and Coding Workshop
Coding Clinic: Questions and Answers Session will focus on the cardiothoracic CPT and ICD coding process
Sidney Levitsky, Boston, MA

Problem Case Presentations (see pp 173–5 for program)

8:15–11:15 **Scientific Session**

23. Mitral Valve Repair for Ischemic Mitral Insufficiency
    William Hendren, James J. Nemec, Bruce W. Lytle, Floyd D. Loop, Paul C. Taylor,
    Robert W. Stewart, and Delos M. Cosgrove III, Cleveland, OH
24. The Edwards Pericardial Aortic Valve: Intermediate Results
    Robert W. M. Frater, Neal W. Salomon, W. Gerald Rainer, and Delos M. Cosgrove III, Bronx, NY
25. Operative Risk and Long-Term Results of Surgery for Left Ventricular Aneurysm
    Masashi Komeda, Azhar Malik, Joan Ivanov, and Tirone E. David, Toronto, Ont, Canada
26. Angioscopic Evaluation of Intravascular Morphology After Coronary Endarterectomy
    Bruce E. Keogh, Benjamin P. Bidstrup, Kenneth M. Taylor, and Ralph N. Sapsford, London, England
27. Total Cavopulmonary Anastomosis Versus the Conventional Modified Fontan Procedure
    Jeffrey M. Pearl, Hillel Laks, Darryl G. Stein, Davis C. Drinkwater, Avedis Meneshian,
    Isabel K. Hartmann, Barbara L. George, and Roberta G. Williams, Los Angeles, CA
28. Current Treatment for Wolff-Parkinson-White Syndrome: Results and Surgical Implications
    Steven F. Bolling, Fred Morady, Hugh Calkins, Alan Kadish, Michael DeBuitleir, Macdonald Dick,
    and Edward L. Bove, Ann Arbor, MI
29. Surgical Therapy of Paroxysmal Atrial Fibrillation Using the "Corridor" Operation
    Jo Defauw, Gerard Guiraudon, Norbert van Hemel, Herre Kingma, Henry van Swieten,
    Jacques de Bakker, and Freddy Vermeulen, Nieuwegein, Netherlands

11:15–12:00 **First Ralph D. Alley Lecture**

The Future of American Thoracic Surgery
Harry Schwartz, PhD, Scarsdale, NY
Columnist for *American Medical News*

Afternoon

1:30–5:00 **Parallel Scientific Sessions**
Session I

1:30–2:45 **General Thoracic II**
Moderator: Peter C. Pairolero, Rochester, MN

30. Acquired Nonmalignant Tracheoesophageal Fistula
    Douglas J. Mathisen, Hermes C. Grillo, John C. Wain, Jr, and Alan D. Hilgenberg, Boston, MA
31. Combined Parietal Cell Vagotomy and Collis-Nissen Fundoplication
    Rodney J. Landreneau, James M. Marshall, Joel A. Johnson, Stephen R. Hazelrigg,
    Theresa M. Boley, and Jack J. Curtis, Columbia, MO
32. Clinical Spectrum of Bronchogenic Cysts of the Mediastinum and Lung in the Adult
    Regent St-Georges, Jean Deslauriers, Andre Duranceau, and Rosaire Vaillancourt, Ste-Foy, Que, Canada
33. Lung Cancer Model to Study Control of the Metastatic Process
    William G. Hammond, Raymond L. Teplitz, and John R. Benfield, Sacramento, CA
34. Improved Management of the Paget-Schroetter Syndrome
    Harold C. Urschel, Jr, and Maruf A. Razzuk, Dallas, TX

3:30–5:00 **Lung Transplant Research**
Moderator: Joel D. Cooper St. Louis, MO

35. Normal Bronchial Healing Without Bronchial Wrapping in Preoperatively and Postoperatively Immunosuppressed Canine Single-Lung Transplantation
    Joseph Auteri, Valluvan Jeevanandam, Juan Sanchez, Thomas Kirby, and Craig Smith, New York, NY
36. A Strategy to Increase the Pulmonary Donor Pool: The Use of Cadaver Lungs for Transplantation
    Thomas M. Egan, C. Jake Lambert, Jr, Blair A. Keagy, and Benson R. Wilcox, Chapel Hill, NC
37. Prolonged Preservation of Dog Lung Allografts: The Role of Prostaglandins
    R. J. Novick, K. R. Reid, L. Denning, J. Duplan, A. H. Menkis, and F. N. McKenzie, London, Ont, Canada

38. Improved Lung Preservation Using UW Solution Compared With Modified Euro-Collins Solution
Stephan Hirt, Thorsten Wahlers, Michael Jurmann, Lutz Dammenhayn, and Axel Haverich, Hannover, Germany

39. Neutrophils Are Not Necessary for Ischemia-Reperfusion Lung Injury
Cynthia N. Steimle, Steven F. Bolling, and G. Michael Deeb, Ann Arbor, MI

40. Pulmonary Granulocyte Sequestration: A Contributor to Pulmonary Injury and Early Failure of the Autoperfused Working Heart-Lung Preparation
Christopher M. Genco, James T. Diehl, Raymond J. Connolly, Karen Ramberg, Eugene Bernstein, Myron B. Peterson, Xi Zhang, and Richard J. Cleveland, Boston, MA

1:30–5:00 **Session II**

1:30–2:45 **Cardiac Research**
Moderator: Timothy J. Gardner, Baltimore, MD

41. Myocardial Oxygen Consumption During Right Heart Bypass
Matthew S. Coons, Thomas T. Woloszyn, Thierry A. Folliguet, Clem Rodriguez, Samir Basu, Joseph N. Cunningham, Jr, and Corrado P. Marini, Brooklyn, NY

42. Recovery of Myocardial Oxygen Utilization Efficiency in Stunned Myocardium
Satoshi Furukawa, Gerhard Kreiner, Joseph Bavaria, James Streicher, and L. Henry Edmunds, Jr, Philadelphia, PA

43. **Thoracic Surgery Directors Association Award Paper**
Determinants of Myocardial Oxygen Consumption in Dilated Cardiomyopathy Influenced by Epinephrine Administration
Cornelius Dyke, K. Francis Lee, Jitendra Parmar, Rebecca Dignan, Thomas Yeh, Jr, Anwar Abd-Elfattah, and Andrew S. Wechsler, Richmond, VA

44. Resuscitation of Injured Myocardium With Adenosine and Biventricular Assist
Todd L. Demmy, James A. Magovern, Race L. Kao, and George J. Magovern, Pittsburgh, PA

45. The Effects of Flow Rate and Temperature on Regional Blood Flow and Oxygen Consumption During Cardiopulmonary Bypass in a Canine Model
W. Douglas Lazenby, Wilson Ko, John A. Zelano, Nathan Lebowitz, Yong T. Shin, O. Wayne Isom, and Karl H. Krieger, New York, NY

3:30–5:00 **Electrophysiology and Cardiac Research**
Moderator: Robert A. Guyton, Atlanta, GA

46. Selective Surgical Approach for Atrioventricular Reentrant Tachycardia
Alexander S. Geha, Lee A. Biblo, Mark D. Carlson, and Albert L. Waldo, Cleveland, OH

47. Effect of Location of AICD Patch Electrodes on Left Ventricular Diastolic Pressure-Volume Curve in Pigs
Joseph S. Auteri, Valluvan Jeevanandam, Juan A. Sanchez, and Henry M. Spotnitz, New York, NY

48. A New Extraaortic Counterpulsation Device
John A. Zelano, Wilson Ko, Richard Lazzaro, W. Douglas Lazenby, Stephen Topaz, Willem J. Kolff, O. Wayne Isom, and Karl H. Krieger, New York, NY and Salt Lake City, UT

49. Retrograde Cerebral Perfusion Through a Superior Vena Cava Cannula Protects the Brain
Akihiko Usui, Toshiro Hotta, Manabu Hiroura, Mitsuya Murase, Masanobu Maeda, Takashi Watanabe, Eiji Takeuchi, Minoru Tanaka, and Toshio Abe, Nagoya, Japan

50. Calcification of Porcine Valves: A Successful New Method of Antimineralization
John Parker Gott, Pan-Chih, Lynne M. A. Dorsey, John L. Jay, Frederick J. Schoen, and Robert A. Guyton, Atlanta, GA

51. Effects of Internal Mammary Artery Dissection on Phrenic Nerve Function and Perfusion
James W. O'Brien, Scott H. Johnson, Scott J. VanSteyn, J. Scott Kabas, Robbin E. Sharpe, and Peter K. Smith, Durham, NC

1:30–5:00 **Session III**

1:30–2:45 **Adult Cardiac II**
Moderator: Delos M. Cosgrove III, Cleveland, OH

52. Improvement in Surgery for Acute Type A Aortic Dissection. Intraluminal Graft, Dacron Prosthesis, or Biological Glue?
J. R. Seguin, J.-M. Frappier, and P. A. Chaptal, Montpellier, France

53. Long-Term Follow-up of Descending Aortic Dissection
John Elefteriades, James Hartleroad, John Baldwin, Richard Gusberg, Henry Black, Gary Kopf, Kenneth Franco, Michael Dewar, and Graeme Hammond, New Haven, CT

54. Advances in the Surgery of the Aortic Arch
Joachim Laas, Michael Jurmann, Markus Heinemann, and Hans Georg Borst, Hannover, Germany

55. A New Extended Vertical Transseptal Atrial Approach for Mitral Valve Surgery in 36 Patients
Gerard M. Guiraudon, Raj Kaushik, John Ofiesh, and Douglas G. McLellan, London, Ont, Canada

56. Prospective Study Using Intraoperative Transesophageal Echocardiography to Grade Atheromatous Aortic Arch Disease: Early Results
Greg H. Ribakove, Edward S. Katz, Aubrey C. Galloway, Rick A. Esposito, Itzhak Kronzon, and Frank C. Spencer, New York, NY

3:30–5:00 **Congenital Cardiac**
Moderator: Adnan Cobanoglu, Portland, OR

57. The Use of an Experimental "One-Way Valved ASD Patch": Animal Studies and Preliminary Clinical Experience
J. Barak and B. A. Vidne, Tel Aviv, Israel

58. The Partial Fontan: Advantages of an Adjustable Interatrial Communication
Jeffrey M. Pearl, Hillel Laks, Davis C. Drinkwater, Darryl G. Stein, Barbara George, and Roberta Williams, Los Angeles, CA

59. Successful Relief of Neonatal Congenital Aortic Stenosis Utilizing Inflow Occlusion
Michael A. Grosso, John St. Cyr, David Fullerton, David N. Campbell, and David R. Clarke, Denver, CO

60. Options for Surgical Treatment of Subaortic Stenosis in the Univentricular Heart
Tom R. Karl, Kevin Watterson, Shunji Sano, and Roger B. B. Mee, Melbourne, Australia

61. Surgical Options in Subaortic Stenosis Associated With Endocardial Cushion Defects
Serafin DeLeon, Michel Ilbawi, William Wilson, Rene Arcilla, Otto Thilenius, Saroja Bharati, Maurice Lev, and Farouk Idriss, Chicago, IL

62. Repair of Truncus Arteriosus in Infancy
Jeffrey M. Pearl, Hillel Laks, Davis Drinkwater, Orrin Ailloni-Charas, Frank Giacobetti, Barbara George, and Roberta Williams, Los Angeles, CA

Evening

7:00 **Reception for Members and Guests**

February 20, 1991 (Wednesday)
Morning

7:00–8:00 **Breakfast Sessions**
No advance registration. Attendance by ticket only and limited to 35 per seminar. Tickets can be purchased at registration desk on Monday, February 18, starting at 12:30 PM. Price of ticket covers attendance at seminar and continental breakfast. These sessions run concurrently.

CPT Nomenclature and Coding Workshop
Coding Clinic: Questions and Answers Session will focus on the cardiothoracic CPT and ICD coding process
Sidney Levitsky, Boston, MA

Clinical Workshops (see pp 175 and 176 for program)

8:15–12:00 **Scientific Session**

63. Laryngotracheoplastic Resection for Subglottic Stenosis: Results of Excision and Primary Reconstruction
Hermes C. Grillo, Douglas J. Mathisen, and John C. Wain, Jr, Boston, MA

64. Surgical Management of Medically Unresponsive Pulmonary Infection With *Mycobacterium tuberculosis* and Other Mycobacterial Organisms
Marvin Pomerantz, Marian Goble, Lori Madsen, and Michael Iseman, Denver, CO

65. Malignant Esophagorespiratory Fistula: Treatment Options and Survival
Michael Burt, William Diehl, Manjit S. Bains, Robert J. Ginsberg, Nael Martini,
Patricia M. McCormack, and Valerie W. Rusch, New York, NY

66. Early Experience of Double Lung Transplantation for Cystic Fibrosis
Hani Shennib, Michel Noirclerc, and the Cystic Fibrosis Transplant Study Group, Montreal, Que, Canada

67. Intraoperative Aortic Dissection
Robert J. Still, Alan Hilgenberg, Cary W. Akins, Mortimer J. Buckley, and Willard M. Daggett, Boston, MA

68. Results of Surgery for Recent Myocardial Infarction Using Warm Aerobic Arrest
Samuel V. Lichtenstein and Tomas A. Salerno, Toronto, Ont, Canada

69. Experience With Surgical Repair of Aortic Root Aneurysms: Results in 280 Patients
Clifton T. P. Lewis, Denton A. Cooley, Oscar Talledo, Michael C. Murphy, and David Vega, Houston, TX

70. Blunt Injuries of the Thoracic Aorta
Alan D. Hilgenberg, Diana L. Logan, Cary W. Akins, Mortimer J. Buckley, Willard M. Daggett,
Gus J. Vlahakes, and David F. Torchiana, Boston, MA

71. Bilateral Latissimus Dorsi Cardiomyoplasty: A New Procedure for Biventricular Hemodynamic Augmentation
James A. Magovern, Anthony P. Furnary, Ignacio Y. Christlieb, Race L. Kao, and
George J. Magovern, Pittsburgh, PA

72. Successful Transplantation of Hearts Harvested 30 Minutes After Death From Exsanguination
Steven R. Gundry, Javier Alonso de Begona, Motohiro Kawauchi, and Leonard L. Bailey, Loma Linda, CA

February 19, 1991 (Tuesday morning)

7:00–8:00 PROBLEM CASE PRESENTATIONS
(10 Simultaneous Sessions)
Session Committee: Delos M. Cosgrove III, Cleveland, OH, and Timothy J. Gardner, Baltimore, MD

SEMINAR I
DIFFICULT CARDIAC REPAIRS
Discussion Leader: Cary W. Akins, Boston, MA

1. A Large Pseudoaneurysm of the Left Ventricle Associated With Mitral Regurgitation
Mohamed Aziz, Ibrahim Abdelmeguid, and Armand Piwnica, Paris, France

2. Mitral Valve Replacement in a Patient With Idiopathic Thrombocytopenic Purpura
Kenneth Richards and Victor A. Ferraris, Albany, NY

3. Acute Myocardial Infarction and Ventricular Septal Defect
Idris Ali, Stephen E. Fremes, George T. Christakis, and Bernard S. Goldman, Toronto, Ont, Canada

SEMINAR II
CARDIAC INFECTIONS
Discussion Leader: Hartzell V. Schaff, Rochester, MN

4. *Staphylococcus aureus* Endocarditis With Pulmonary Edema, Cerebral and Systemic Embolization in a 26-Year-Old Man
Hugh Scully, Xavier Mousset, John Mullen, and Paul Petrasek, Toronto, Ont, Canada

5. Infective Endocarditis in Patients With Left Ventricular Aneurysm
   Azhar Malik, Masashi Komeda, and Tirone E. David, Toronto, Ont, Canada
6. Bioprosthetic Valve Endocarditis
   George T. Christakis, Idris Ali, Stephen E. Fremes, and Bernard S. Goldman, Toronto, Ont, Canada

SEMINAR III

CORONARY

Discussion Leader: Ellis L. Jones, Atlanta, GA

7. A 7-cm Ruptured Aneurysm of the Right Coronary Artery
   R. Vijayanagar, Paul F. Eckstein, Rafael Salas, Marshall DeSantis, Raymond S. Waters, and Akshay Desai, Tampa, FL
8. Unrecognized Coronary Ostial Stenosis
   Richard Bloom, Idris Ali, George Christakis, and Bernard Goldman, Toronto, Ont, Canada
9. Acute Cardiovascular Collapse After Routine CABG: Possible Protamine Sulfate Hypersensitivity in a Young Man With Vasectomy 10 Years Before
   Sam Hunter and Arlen Holter, Minneapolis, MN

SEMINAR IV

GREAT VESSELS

Discussion Leader: Randall B. Griepp, New York, NY

10. Acute Ascending Aortic Dissection Involving Right Coronary Artery
    Joseph S. Coselli, Houston, TX
11. Ascending Aortic Dissection During Coronary Revascularization
    Richard M. Engelman, John A. Rousou, Joseph E. Flack III, and David W. Deaton, Springfield, MA
12. Pseudoaneurysm of the Innominate Artery
    Julian Belisle, James T. Diehl, Richard J. Cleveland, John Waciuma, and Lynn Welchel, Boston, MA

SEMINAR V

CONGENITAL

Discussion Leader: Kevin Turley, San Francisco, CA

13. Pulmonary Venous Obstruction After Repair of Total Anomalous Pulmonary Venous Connection
    Christo I. Tchervenkov, Jerome B. Riebman, Marie J. Beland, and Anthony R. C. Dobell, Montreal, Que, Canada
14. Ebstein's Anomaly, VSD and Pulmonary Hypertension Presenting in Infancy
    Tom R. Karl and Roger B. B. Mee, Melbourne, Australia
15. Isolated Unilateral Pulmonary Artery Agenesis and Necrotizing Pneumonia in a Neonate
    Charles C. Canver, John D. Pigott, and Robert M. Mentzer, Jr, Buffalo, NY

SEMINAR VI

AIRWAYS

Discussion Leader: Douglas J. Mathisen, Boston, MA

16. Treatment of Diffuse Tracheomalacia
    George B. Haasler, Milwaukee, WI
17. Tracheal Complication of Transhiatal Esophagectomy
    L. A. Gorenstein, J. G. Abel, and G. A. Patterson, Toronto, Ont, Canada
18. Complex Rupture of Major Airways
    A. G. Justicz and P. N. Symbas, Atlanta, GA

SEMINAR VII

CHEST WALL AND MEDIASTINUM

Discussion Leader: Victor F. Trastek, Rochester, MN

19. Anterior Superior Mediastinal Mass With Superior Vena Cava Syndrome
    Warren A. Williamson, John M. Streitz, Jr, and David M. Shahian, Burlington, MA

20. Lymphangiectasis of the Mediastinum With Chylothorax and Chylopericardium
    Himmet Dajee, John Eilbert, Viney Soni, and Glen Justice, Newport Beach, CA
21. Chest Wall Tumor of Fifth Rib Posteriorly
    C. Frederick Kittle, Chicago, IL

SEMINAR VIII
ESOPHAGUS
Discussion Leader: Mark K. Ferguson, Chicago, IL

22. Drainage and Irrigation Technique as a Primary Treatment for Late Presentation of Spontaneous Esophageal Rupture
    Shlomo Gabbay, Nezih Ozdemir, Robert J. Wilcott, and James N. Heller, Newark, NJ
23. Management of Esophagopulmonary Fistula in a Patient With Megaesophagus Secondary to Achalasia
    David G. Kitts, George E. Cimochowski, Jeffrey C. Milliken, and Russell A. Williams, Torrance, CA
24. Esophagopericardial Fistula Four Years After Radiotherapy for Esophageal Cancer
    Paul F. Waters, Los Angeles, CA

SEMINAR IX
PULMONARY 1
Discussion Leader: Larry R. Kaiser, St. Louis, MO

25. Surgical Management of Aspergilloma and Hemoptysis
    J. W. Randolph Bolton and Harold L. Lazar, Boston, MA
26. Massive Wheat Grain Aspiration—A Survivor
    W. T. Kidd and P. E. Blundell, Montreal, Que, Canada
27. Complications of Group A Streptoccocus Pneumonia
    Michael P. Koumjian, Lucien N. Jassy, and William E. Mora, LaMesa, CA

SEMINAR X
PULMONARY 2
Discussion Leader: Thomas Rice, Cleveland, OH

28. Postpneumonectomy Tension Chylothorax
    Julian Belisle, Irving Madoff, and James T. Diehl, Boston, MA
29. Bronchogenic Carcinoma With Empyema
    Darryl S. Weiman, L. Michael Graver, and Denis H. Tyras, New Hyde Park, NY
30. Late Complication of Plombage
    Michael D. Horowitz and Richard J. Thurer, Miami, FL

Wednesday, February 20, 1991

7:00–8:00 CLINICAL WORKSHOPS
(10 Simultaneous Sessions)
Session Committee: Adnan Cobanoglu, Portland, OR, and Douglas J. Mathisen, Boston, MA

WORKSHOP I
MANAGEMENT OF STAGE III LUNG CANCER
Alex G. Little, Las Vegas, NV

WORKSHOP II
TRACHEOBRONCHIAL TRAUMA
Jean Deslauriers, Ste-Foy, Que, Canada

WORKSHOP III
MANAGEMENT OF MEDIASTINAL MALIGNANCIES
Robert J. Ginsberg, New York, NY

WORKSHOP IV
TECHNICAL CONSIDERATIONS OF ESOPHAGEAL SUBSTITUTES
Richard F. Heitmiller, Baltimore, MD

WORKSHOP V

ALTERNATIVE CONDUITS FOR CORONARY REVASCULARIZATION
Noel L. Mills, New Orleans, LA

WORKSHOP VI

OPERATIVE INTERVENTION IN ATRIAL FIBRILLATION
James L. Cox, St. Louis, MO

WORKSHOP VII

MITRAL VALVE REPAIR
Steven B. Colvin, New York, NY

WORKSHOP VIII

REPEAT OPERATION FOR CORONARY REVASCULARIZATION
Bruce W. Lytle, Cleveland, OH

WORKSHOP IX

HOMOGRAFT USE IN INFANTS AND CHILDREN
John J. Lamberti, San Diego, CA

WORKSHOP X

THE ARTERIAL SWITCH OPERATION
William G. Williams, Toronto, Ont, Canada

THE
ANNALS OF
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SURGERY

*Official Journal of The Society of Thoracic Surgeons
and the Southern Thoracic Surgical Association*

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Esophageal and Foregut Disorders: Pathophysiology and Treatment, Big Island of Hawaii—January 24–29, 1991

For information on this meeting, contact Department of Surgery, Creighton University, CME Program, 601 N 30th St, Omaha, NE 68131; or telephone (402) 280-4501 (facsimile: (402) 280-4593).

Twenty-seventh Annual Meeting of The Society of Thoracic Surgeons, San Francisco, California—February 17–20, 1991

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610.

Lung Transplantation—An International Dialogue, Laguna Niguel, California—February 20–22, 1991

For information on this meeting, contact Cedars-Sinai Medical Center, Continuing Medical Education, Room 2727, PO Box 48750, Los Angeles, CA 90048; or telephone (213) 855-5547.

Pathophysiology & Techniques of Cardiopulmonary Bypass, San Diego, California—February 22–24, 1991

For information on this meeting, contact Cardiothoracic Research & Education Foundation, PO Box 23220, San Diego, CA 92193; or telephone (619) 541-1444.

Team Approach to Pediatric Cardiac Disease, Beaver Creek/Vail, Colorado—February 24–27, 1991

For information on this meeting, contact David R. Clarke, MD, Cardiothoracic Surgery, B-200, The Children's Hospital, 1056 East 19th Ave, Denver, CO 80218; or telephone (303) 861-6665.

Fortieth Annual Meeting of the American College of Cardiology, Atlanta, Georgia—March 3–7, 1991

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

First International Symposium on Diseases of the Aorta, Tokyo, Japan—March 6–8, 1991

For information on this meeting, contact Secretariat of ISDA, c/o Japan Convention Services, Inc, Nippon Press Center Bldg, 2-2-1, Uchisaiwai-cho, Chiyoda-ku, Tokyo 100, Japan.

Arrhythmia Surgery Operative Clinics, St. Louis, Missouri—March 21–23, 1991, and October 3–5, 1991

For information on these meetings, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

Neonatal Cardiac Surgery for Transposition of the Great Arteries, Plessis-Robinson, France—March 24–28, 1991

For information on this meeting, contact Aloma Wybenga, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

General Thoracic Surgery, Boston, Massachusetts—April 22–23, 1991

For information on this meeting, contact the Department of Continuing Education, Harvard Medical School, PO Box 825, Boston, MA 02117; or telephone (617) 432-1525.

Myocardial Assist Techniques Seminar I, Washington, DC—May 2–3, 1991

For information on this meeting, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

Seventy-first Annual Meeting of The American Association for Thoracic Surgery, Washington, DC—May 6–8, 1991

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Quality of Life After Open Heart Surgery, Antwerp, Belgium—May 16–18, 1991

This meeting is sponsored by The World Health Organization, the European Society of Cardiology, and the International Society and Federation of Cardiology. For information on this meeting, contact P. J. Walter, MD, FACS, Professor and Chairman of the Department of Cardiovascular Surgery, University Clinic of Antwerp, B 2520 Antwerp, Wilrijkstraat 10, Belgium; or telephone 00323.829.11.11 (facsimile: 00323.830.20.99).

Vascular Surgery 1991—Current State of the Art, New York, New York—May 16–18, 1991

For information on this meeting, contact Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042; or telephone (718) 470-8650.

Coronary Surgery: Clinical and Basic Perspectives, Sheffield, England—May 17, 1991

For information on this meeting, contact G. D. Angelini, Clinical Sciences Centre, Northern General Hospital, Herries Rd, Sheffield S5 7AU, England.

Surgery for Coronary Artery Disease, Durham, North Carolina—May 20–21, 1991

For information on this meeting, contact Vanessa Moore, PO Box 2986, Duke University Medical Center, Durham, NC 27710, or telephone (919) 684-6077; or contact American College of Cardiology, Extramural Programs Department, 9111 Old Georgetown Rd, Bethesda, MD 20814, or telephone (800) 253-4636.

Fifth International Symposium on Cardiac Bioprostheses, Avignon, France—May 24–27, 1991

This meeting is sponsored by the Scientific Committee for the Advancement of Cardiac Bioprostheses. For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870.

Ninth World Symposium on Cardiac Pacing and Electrophysiology, Washington, DC—May 28–31, 1991

This meeting will incorporate the Twelfth Annual Scientific Session of the North American Society of Pacing and Electrophysiology. For information on this meeting, contact IXth World Symposium Secretariat, c/o NASPE, 377J Elliot St, Newton Upper Falls, MA 02164; or telephone (617) 237-1866 (facsimile: (617) 431-1991).

The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Boston, Massachusetts—June 3–5, 1991

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Cardiac Arrhythmia Surgery International Seminar II, Geneva, Switzerland—June 12–14, 1991

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

Seventeenth Annual Meeting of The Western Thoracic Surgical Association, Seattle, Washington—June 26–29, 1991

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Twentieth World Congress of The International Society for Cardiovascular Surgery, Amsterdam, the Netherlands—September 1–6, 1991

For information on this meeting, contact the Registrar: XX World Congress—ISCVS, International Travel Service, Inc, 104 Wilmot Rd, Suite 300, PO Box 825, Deerfield, IL 60015; or telephone (708) 940-2100 (facsimile: (708) 940-2386); or contact the Congress Secretariat, International Society for Cardiovascular Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Fifth Annual Meeting, European Association for Cardio-Thoracic Surgery, London, United Kingdom—September 22–25, 1991

For information on this meeting, contact Organising Secretariat, Conference Associates & Services, Ltd, Congress House, 55 New Cavendish St, London W1M 7RE United Kingdom; or telephone 071 486 0531 (facsimile: 071 935 7559; telex: 934 346 CONFAS G).

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Arthur Carlucci, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010 (telephone: (212) 633-3806; facsimile: (212) 633-3880). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.25 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $17.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3853). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad. To respond to an anonymous ad, write to Box Number, *The Annals of Thoracic Surgery*, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

SITUATIONS AVAILABLE

Cardiac surgeon, board certified or board eligible, for very busy private practice group doing primarily adult cardiac and vascular surgery. Seeking an Associate to join well-established practice in northeast Ohio metropolitan area. Please respond with curriculum vitae and references.

Please respond to Box 370. 370H/A

Cardiothoracic surgeon, ABTS certified/eligible, with primary interest in cardiac surgery, wanted immediately to replace member of established surgical group practicing in Allentown, PA. Competitive salary/fringe benefits. Position leads to partnership for successful candidate.

Please send curriculum vitae, clinical experience, and references to Joan M. Persa, Administrator, 1275 South Cedarcrest Blvd, Allentown, PA 18103; (215) 821-8790. 393I/B

Cardiovascular and thoracic surgeon: BE/BC wanted to join well-established private group practice in Philadelphia area. Seek recent or upcoming graduate. Please send curriculum vitae.

Please respond to Box 394. 394I/B

Cardiovascular surgeon to become second surgeon in new (two year old) adult cardiac program on west coast of Florida.

Submit CV to Manatee Cardiac Surgeons, PA, 201 4th Ave East #2, Bradenton, FL 34208. 396I/B

Cardiovascular surgeon, board certified/eligible, wanted to join two surgeons in an established cardiovascular program in the southeastern USA. Must have experience in adult cardiac, thoracic, and vascular surgical procedures. Salary/full partnership negotiable. Please send resume.

Please respond to Box 398. 398I/B

Thoracic/vascular surgeon needed to join prominent, active 3-man group in desirable suburban community in greater NY metropolitan area. Excellent opportunity for well-trained, highly motivated individual. Recent graduate preferred. Possible academic affiliation. Please respond with CV.

Please respond to Box 404. 404J/C

Thoracic and cardiovascular surgeon, board certified or eligible, wanted for an established practice in the Midwest with experience in adult cardiac, thoracic, and peripheral vascular surgery. Experience or training in heart/lung transplantation preferred. Initial contact should include curriculum vitae, clinical experience, and names of references.

Please respond to Box 408. 408J/B

Cardiac surgeon—board certified/eligible to be third member of established practice in suburb of Washington, DC, expanding to second hospital. Excellent compensation and benefits. Great opportunity for recent graduate wishing to locate in area of nation's capital. Practice focus is primarily in adult cardiac surgery with additional work in thoracic and peripheral vascular surgery available.

Please send curriculum vitae to PO Box 34945, Bethesda, MD 20817. 415J/C

Cardiothoracic/vascular surgeon: board certified in general and thoracic surgery. Minimum of 2 years of practice experience. Very active private multispecialty practice. Located in western Pennsylvania. Salary leading to full partnership. Excellent benefits. Detailed CV must accompany response. All replies treated confidentially.

Please respond to Box 419. 419J/C

Cardiothoracic surgeon needed to join established 2-man group in practice of adult cardiac, pulmonary, and vascular surgery. Must be board certified or eligible and graduate from a US medical school.

Please respond to R. W. Ruess, MD, 1834 Broadway, Cape Girardeau, MO 63701. 422J/C

Cardiovascular-thoracic surgeon—BE/BC to join established and growing 2-surgeon group in northeastern US. Practice includes high volume cardiac and general thoracic surgery. Recent trainee preferred. Submit CV.

Please reply to Box 423. 423J/C

Cardiothoracic surgeon wanted for busy, expanding private practice in Connecticut. Practice includes cardiac and thoracic surgery. Surgeon must be board eligible or certified. Excellent opportunity for suitable applicant.

Please respond to Box 424. 424K/A

Pacific Northwest opportunity for cardiothoracic surgeon with 2 to 4 years of experience. Growing multispecialty group practice in Portland, Oregon, seeks dynamic surgeon to join 3 other surgeons in our practice. General thoracic and vascular experience necessary.

Please send curriculum vitae to Dr James W. Asaph, MD, 507 NE 47th Ave, Portland, OR 97213-2282. 426K/D

Cardiothoracic surgeon, recent graduate, experienced in cardiac arrhythmia surgery, to join well-established cardiac surgical group in central Florida. Send CV.

Please respond to Box 427. 427K/A

Cardiac surgeon wanted to join established private practice in upstate New York, primarily adult cardiac. Board certified or eligible required. New or recent graduate preferred. Please send CV and references.

Please respond to M. A. Marvasti, MD, 101 Union Ave, #813, Syracuse, NY 13203. 429K/D

Wanted: BE/BC general surgeon with interest and experience in thoracic surgery who enjoys general surgery, or non-cardiac thoracic surgery, to assume practice of retiring double-boarded thoracic/general surgeon. 34-member multispecialty group in dynamic area hub city of 35,000, with six satellite offices in strategic locations and referral area of 300,000 plus. Superb hospital facilities, including CT, MRI, cardiac surgery, neurosurgery, etc. Directed towards those concerned about quality family lifestyle and professional concerns.

Contact Recruitment Coordinator, Park Clinic, 890 North Eisenhower Ave, Mason City, IA 50401; or dial 800-798-4321 for more information. 431K/D

Cardiovascular/vascular surgeon wanted to join busy established adult practice in Ohio. Recent graduate preferred. Please submit curriculum vitae. Association will lead to partnership.

Please respond to Box 436. 436K/C

BC/BE adult cardiothoracic surgeon wanted to join active established department in large multispecialty group practice located in metropolitan Midwest community. Medical school affiliation available. Respond with curriculum vitae.

Please respond to Box 437. 437K/D

Minneapolis cardiothoracic/vascular group seeks to add fifth surgeon, BC/BE.

Respond to BLH Physician Search, 2231 Lee Ave N, Minneapolis, MN 55422; (612) 588-1116 or -0333. 438L/E

Board certified/eligible cardiothoracic surgeon for busy 1-physician practice in Atlanta. Transplant experience. Future partnership.

Send resume to Georgia Cardiac Surgical Association, PO Box 491203, College Park, GA 30349. 439L/E

Thoracic surgeon, BE/BC, wanted to join 4-man group on Gulf Coast of Florida, specializing in general, vascular, and noncardiac thoracic surgery. Recent graduate preferred. Please send CV and references.

Please respond to Box 441. 441L/B

Cardiothoracic surgeon wanted for July 1991: expanding private practice in Philadelphia. Adult cardiac and thoracic surgery. Academic appointment. Eventual partnership.

Send CV and references to PO Box 1295, Philadelphia, PA 19105. 442L/B

Cardiovascular and thoracic surgeon, BC/BE: Exciting academic position available for the initiation of a cardiac transplant program, participation in ongoing clinical and basic science research, and a busy clinical cardiac and thoracic surgical practice. An extremely competitive salary and benefit package is available.

Candidates should forward a letter of application and CV to Cardiovascular and Thoracic Surgery, University of Kentucky Medical Center, 800 Rose St, Lexington, KY 40536-0084. 448L/A

Wanted—thoracic surgeon, BE/BC, to join a board certified surgeon for noncardiac thoracic surgery and peripheral vascular surgery in a growing medical center in upstate New York.

Please respond to Box 451. 451L/B

Chief, Cardiothoracic Surgery: Excellent opportunity to lead cardiothoracic surgery department for 400-bed community teaching hospital located in western Pennsylvania. This dynamic facility performs 900 open heart procedures and 5,600 catheterizations per year. Qualified candidates should possess academic credentials and have interest in developing clinical research.

Please contact Jeanne Dowrick, Fulton, Longshore and Associates, Inc, 527 Plymouth Rd, Plymouth Meeting, PA 19462; telephone (800) 346-8397 or (215) 834-6780. 453L/B

Thoracic and vascular surgeon needed—Southeast: Looking for a partner to join an established surgeon to practice noncardiac thoracic and vascular surgery in mid-sized city. Must be board certified or eligible. No buy-in needed, guaranteed income available. Excellent community to raise a family with the cultural advantages of a large city but not the hassles. Will consider others, but recent graduate preferred. Send CV, and include description of interests, and career goals.

Please respond to Box 454. 454L/C

Cardiovascular and thoracic surgeon: Position available for a board certified or eligible cardiovascular and thoracic surgeon to join a 2-man private practice involved with adult cardiac, thoracic, and peripheral vascular surgery in a desirable eastern metropolitan area. Association features competitive salary, excellent fringe benefits, and a goal of early partnership. Please send curriculum vitae.

Please respond to Box 455. 455L/B

Surgeon with interest/experience in hemodialysis access to manage 400–450 cases per year as part of a large, established, mid-Atlantic cardiovascular and thoracic surgical practice. ABS required; salary, incentives, and call schedule negotiable. Send CV.

Please respond to Box 456. 456L/B

Cardiothoracic surgeon interested in joining an established practice in the Southwest. Must be experienced in adult cardiac, pulmonary, and vascular surgery. Must be board certified/board eligible. Please respond with curriculum vitae.

Please respond to Box 457. 457L/C

Thoracic and cardiovascular surgeon wanted to join a busy practice. Prefer recent graduate. Must be board certified or eligible. Located in Midwest. Please respond with curriculum vitae.

Please respond to Box 458. 458L/B

Cardiovascular and thoracic surgeon, BE/BC, to join another physician in a rapidly expanding private practice located in the Southeast. Please send curriculum vitae and references.

Please respond to Box 459. 459L/E

University of Massachusetts Medical Center is recruiting candidates for its newly opened Cardiothoracic Surgical Residency Program for 1991, 1992, and 1993. The applications for the 1993 position will be processed through the Match Program for Cardiothoracic Residencies.

Request applications from and submit curriculum vitae and three letters of recommendation to Thomas J. Vander Salm, MD, Chief, Division of Cardiothoracic Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655; telephone: (508) 856-2216. 462L/E

Cardiac surgeon, board certified or eligible, needed for a growing cardiac surgery program in the Southeast. Excellent opportunity for someone primarily interested in adult cardiac surgery.

Please respond to Box 464. 464L/A

Cardiovascular-thoracic surgeon, BC/BE, needed to join busy expanding private practice in the Midwest. Excellent program, large number of experienced cardiologists. Initial contact should include curriculum vitae and references. Ideal candidate will have results to submit.

Please respond to Box 466. 466A

Cardiovascular surgeon to join another physician in partnership. Lucrative practice opportunity. *Must do* comprehensive cardiovascular *and* thoracic procedures. On staff at five major hospitals. Two offices and staff in place. Must be able to establish new lines of referral. State-of-the-art pacemaker clinic in office. Suburban location near Chicago, IL (population of 5 million) is 25 minutes due west of downtown. $175,000 first year salary plus pension, buy-in, and other benefits.

Send CV or call David Cornett, Jackson and Coker, Inc, 115 Perimeter Center Place, Suite 380 10031, Atlanta, GA 30346; telephone: 1-800-544-1987. 467A/C

Assistant/Associate Professor needed for expanding *cardiothoracic surgery* program. Position involves primarily adult cardiac surgery with some thoracic. Experience/interest in electrophysiology advantageous. Commitment to research and teaching essential. Exceptional opportunity for academic development in a desirable community. USF is an EEO/AA employer.

Please send CV to Peter P. McKeown, Chief of Cardiovascular & Thoracic Surgery, University of South Florida, #730, 4 Columbia Dr, Tampa, FL 33606. 469A/C

Cardiac surgeon, board certified. Minimum 5 years experience in adult cardiac surgery to join 2-surgeon practice in Southeast. Send CV.

Please respond to Box 471. 471A/C

Assistant surgeon sought for busy adult cardiothoracic surgery practice. Entire responsibility will be to assist four senior surgeons in the operating room. Board certification or eligibility in general surgery, and some experience in vascular and/or thoracic surgery, desirable. Must be licensed in Pennsylvania or able to obtain license. Generous salary and fringes. Position is available immediately and could be permanent. Ideal location in very pleasant, small city near major eastern metropolitan centers.

Please respond with CV to Lawrence I. Bonchek, MD, 555 North Duke St, Lancaster, PA 17603; (717) 295-8395. 472A/B

Thoracic-cardiovascular surgeon to establish a cardiovascular program in an acute care facility located in the Midwest. In place is the certificate of need, catheterization laboratory, heart suites, 10-bed CCU as well as a 10-bed ICU. This heart program will be the prime program in a multicounty serving area. Compensation will reflect candidate's certification and experience.

Please respond to Box 475. 475A

Cardiothoracic surgeon, board eligible/board certified, to join expanding academic practice at The Medical College of Pennsylvania. Excellent clinical and investigational facilities available with ample opportunities for clinical or basic science research. Solid general surgery residency with active medical student participation. Practice includes valve repairs, electrophysiologic surgery, transplantation. Salary very competitive.

Please send curriculum vitae to Glenn Whitman, MD, The Medical College of Pennsylvania, 3300 Henry Ave, Philadelphia, PA 19129 or call (215) 842-6564. 476A/B

Cardiothoracic/vascular surgeon, BE/BC, wanted to join growing practice in New Jersey. Recent graduate preferred. Please respond with CV.

Please respond to Box 477. 477A/C

Cardiovascular thoracic surgeon—board certified/board eligible and recently trained to join an established, busy, dynamic, and expanding private practice in northwest Indiana. The sphere of practice is approximately 30 minutes from downtown Chicago. Guaranteed excellent starting salary with progressive future growth and comprehensive corporate fringe benefit program.

Write including CV and details of experience and capabilities to PO Box 3066, Munster, IN 46321. 478A/B

Thoracic and vascular surgeon, board certified, to join active (noncardiac) thoracic and vascular practice in northern New Jersey. Competitive salary and benefits. Please respond with curriculum vitae.

Please respond to Box 481. 481A/C

Cardiothoracic surgeon, BC/BE, to join an extremely busy and rapidly expanding solo practice of predominately adult cardiac surgery in a medium-size southern city serving as a regional referral center. Unusually high quality medical care in this outstanding community. Excellent opportunity for a new or recent graduate with generous compensation package leading to early partnership. Please send CV.

Please respond to Box 482. 482A/C

Cardiovascular and thoracic surgeon, BE/BC, wanted to join a busy private practice in Pittsburgh, PA. Please respond with curriculum vitae and details of experience.

Please respond to Box 483. 483A/C

SITUATIONS WANTED

Cardiovascular and thoracic surgeon, university trained, 39, hard working, proficient in valve repairs, IMA grafting, redo surgery, experienced, wishes to relocate. Also available, cardiovascular anesthetist or intensivist to make self-sufficient team to start new practice. All inquiries handled with strictist confidence.

Please respond to Box 428. 428K/A

Cardiovascular/thoracic surgeon, 52, university trained. Busy private practice in same location for 20 years. Established cardiac program, President of Medical Staff, ABS/ABTS, vascular board, critical care board. Seeks private practice opportunity due to local hospital merger.

Please respond to Box 450. 450L/A

Cardiovascular and thoracic surgeon, 39, ABS, ABTS, excellent technique and results, personable. Seeks opportunity with new program or group practice.

Please respond to Box 468. 468A/D

Cardiothoracic and vascular surgeon, 44, ABS, ABTS wishes to relocate. Extensive experience in cardiac, thoracic, and vascular surgery. Would be interested in starting new program or association with established practice. Curriculum vitae and references upon request.

Please respond to Box 479. 479A/C

FELLOWSHIPS

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819. 480A/F

Fellowship in pediatric cardiovascular surgery available July 1991. Experience includes surgery for hypoplastic left heart syndrome and arterial switch. A large, well-organized collection of heart specimens available for review. Illinois license or equivalent required. Salary and benefits in the high $40s.

Please respond to Division of Pediatric Cardiac Surgery, The Heart Institute for Children, Christ Hospital and Medical Center, 4440 W 95th St, Oak Lawn, IL 60453. 443L/C

Surgical residents/fellows—Clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart & Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, ext. 359. 445L/A

Fellowship in cardiovascular surgery: Fellowships for 1 to 2 years with busy service performing many complex cardiac procedures. 1989 cases—1,300. Opportunity to rotate in pediatric service. Foreign graduates must have ECFMG/FMGMS or be eligible for H-1 visa. US and Canadian graduates must be eligible for Oregon licensure.

Please send complete CV to Dr Albert Starr, 9155 SW Barnes Rd, Suite 240, Portland, OR 97225. 452L/B

Cardiopulmonary surgery fellow: July 1991 opening of a clinical position for 1 year in a busy university service that performs cardiac and thoracic surgery, pediatric heart surgery, and cardiac transplantation. The fellow will be given responsibilities in perioperative care and as assistant and operating surgeon based on prior experience. Ideal position for a senior surgical resident who would like to attain additional experience in cardiopulmonary surgery or a resident waiting to enter a thoracic surgery residency.

Please respond with curriculum vitae to Adnan Cobanoglu, MD, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098. 460L/A

A 2-year Cardiovascular Research Fellowship position is available 7/1/91 in the Division of Cardiothoracic Surgery at the University of Massachusetts Medical Center. This is an opportunity for a closely supervised and highly productive cardiac research experience. Requirements: (1) A minimum of 2 years of surgical training; (2) a commitment from an institution to complete the applicant's training in general surgery; (3) intentions to pursue an academic career in cardiothoracic surgery.

Interested candidates should contact Marc S. Visner, MD, Division of Cardiothoracic Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655; telephone: (508) 856-2975. 461L/E

Lung transplantation fellowship: The joint Montreal-Marseille Lung Transplant Program offers fully qualified surgeons an opportunity to spend 6 months each in Montreal and Marseille. Fellows will participate in donor and recipient selection, procurement, transplantation of single, double, and heart/lungs, and early and long-term care of recipients. The fellowship includes an opportunity to develop in-depth knowledge of the basic science of transplantation through intense courses given at McGill Center for Clinical Immunobiology and Transplantation. Hands-on experience in management of airway problems including bronchial laser and stent therapy under the supervision of Professeur J. F. Dumon will also be provided. An additional year of basic research experience is optional.

Please respond to Dr H. Shennib, Director, McGill Lung Transplant Program, Montreal General Hospital, 1650 Cedar Ave, Montreal, Que, Canada H3G 1A4. 470A/B

Cardiac surgical fellowship available at medical center doing a large volume of adult cardiac surgical procedures; program affiliated with the University of Miami, Florida. Medical license necessary, ideal for board eligible/certified general surgeon awaiting thoracic residency of board-eligible individual in thoracic surgery seeking additional experience.

Please respond with CV to Donald B. Williams, MD, Department of TCVS, Mount Sinai Medical Center, Miami Beach, FL 33140. 473A/C

Fellowship, cardiopulmonary transplantation: Busy heart, heart-lung, and lung transplant center performing 45–50 transplantations a year requires a board eligible/certified thoracic surgeon to work as a Transplant Fellow commencing July 1991. Responsibilities will include donor and recipient operations, postoperative care, and participating in ongoing experimental and clinical research protocols.

Contact Dr Neil McKenzie, University Hospital, PO Box 5339, London, Ont, Canada N6A 5A5. 474A

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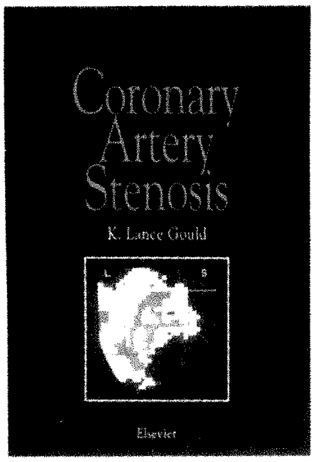

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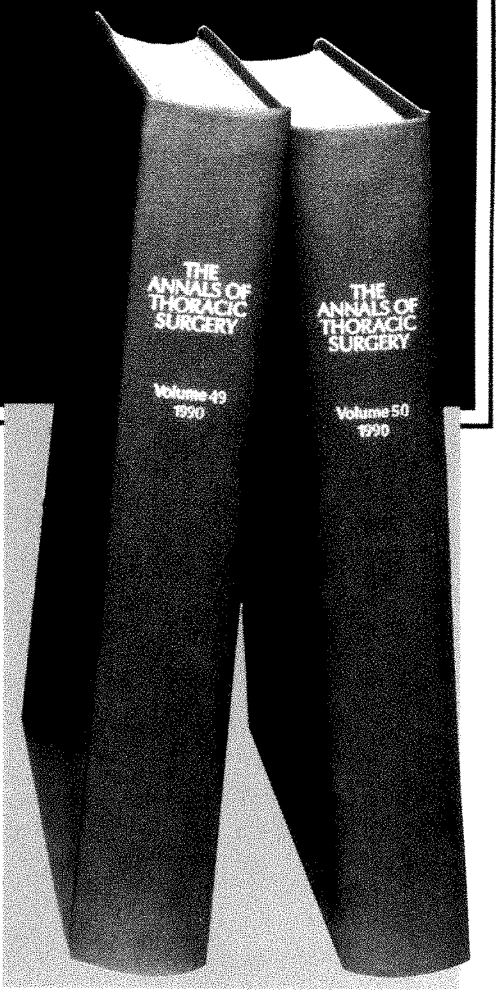
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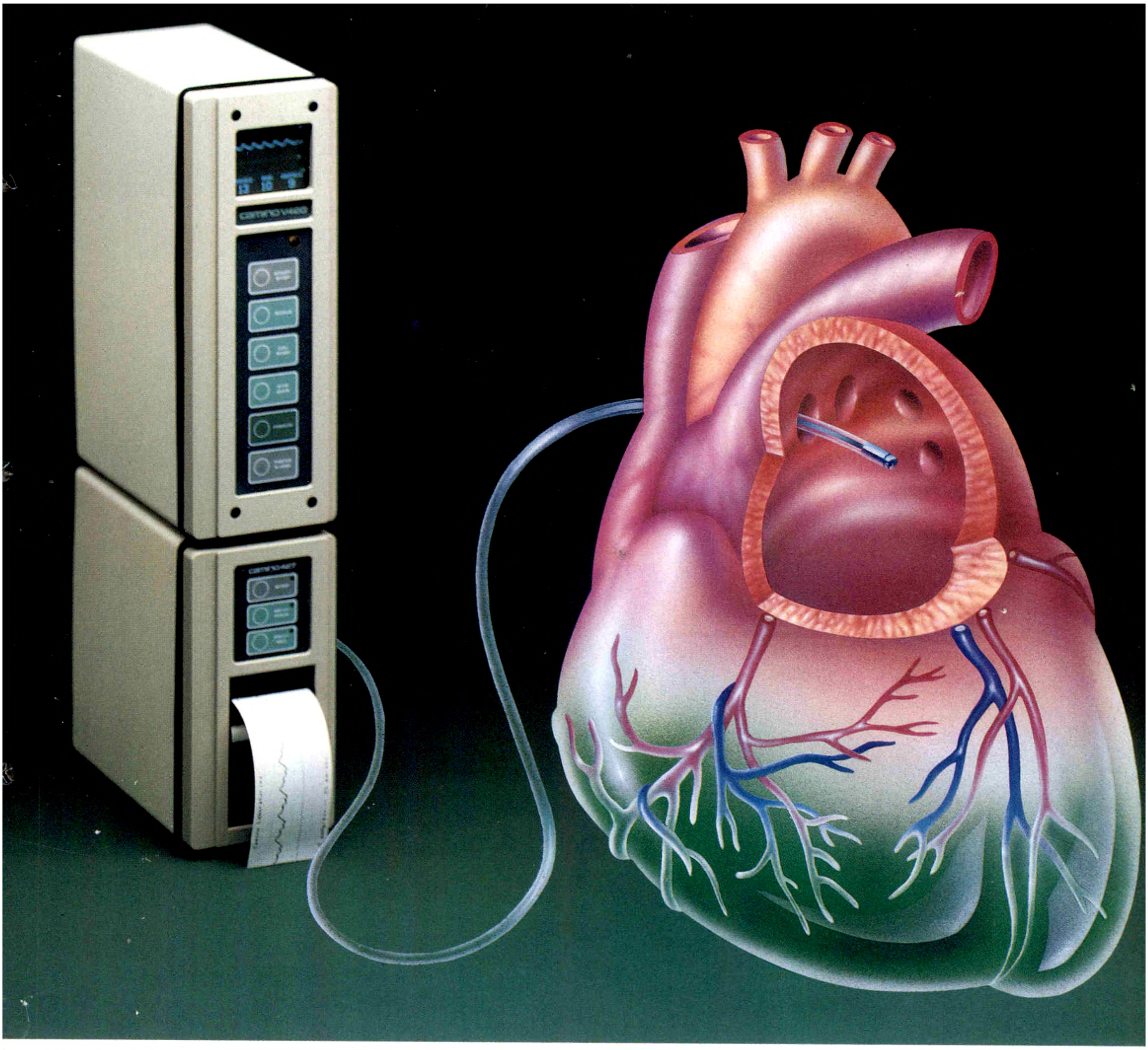

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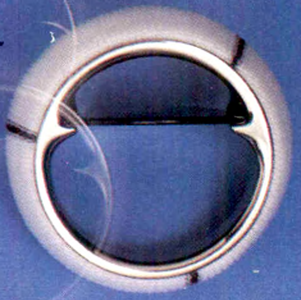

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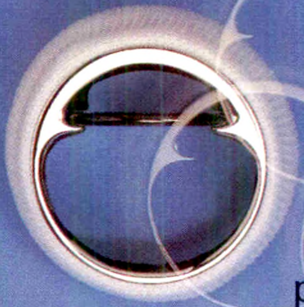

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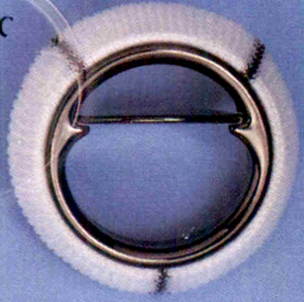

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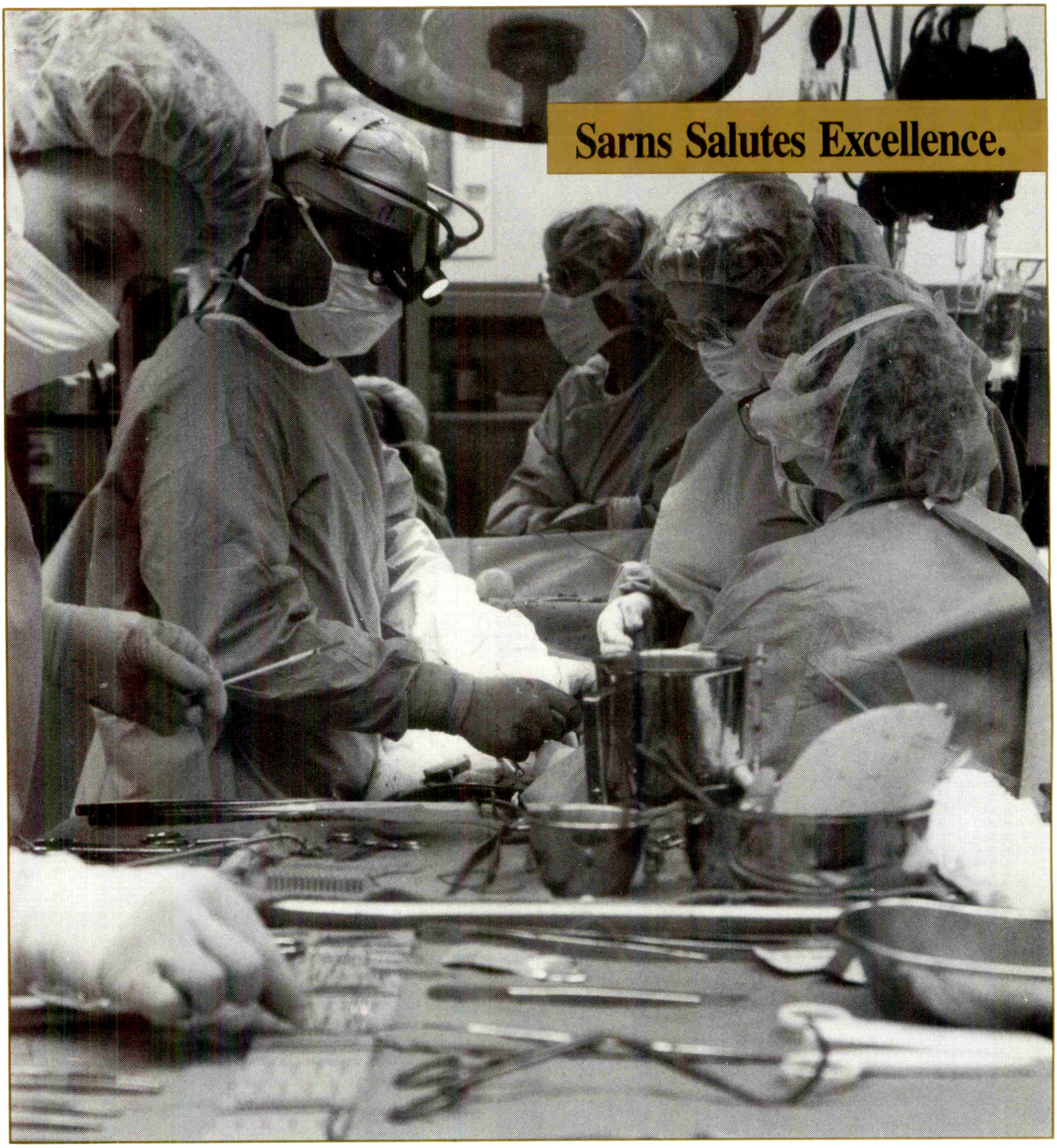
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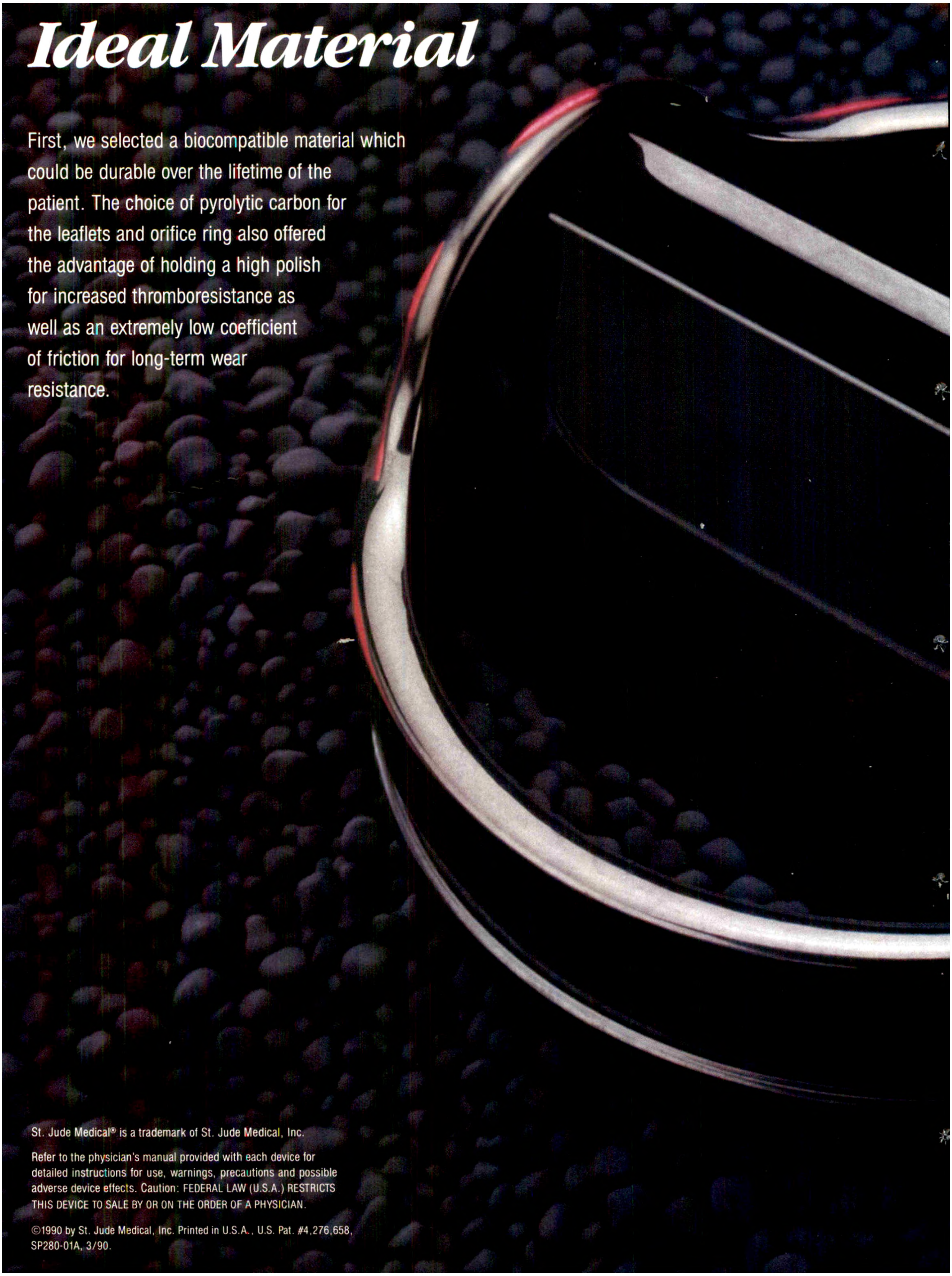

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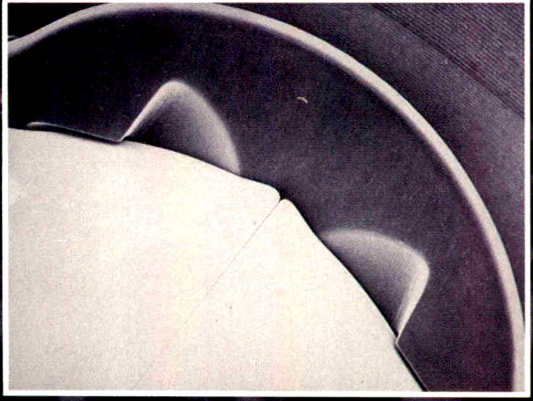

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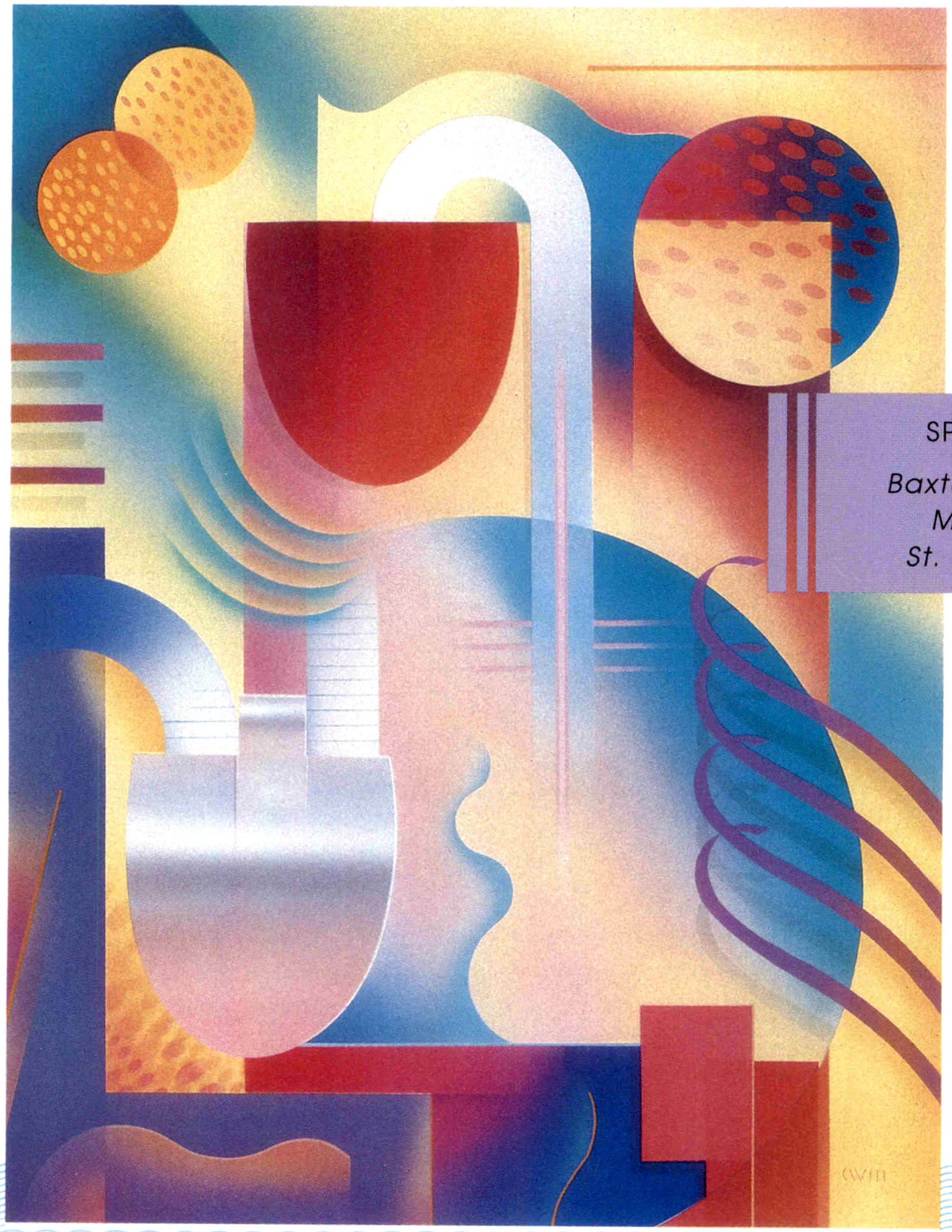

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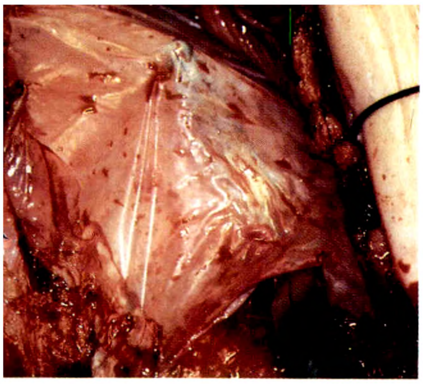

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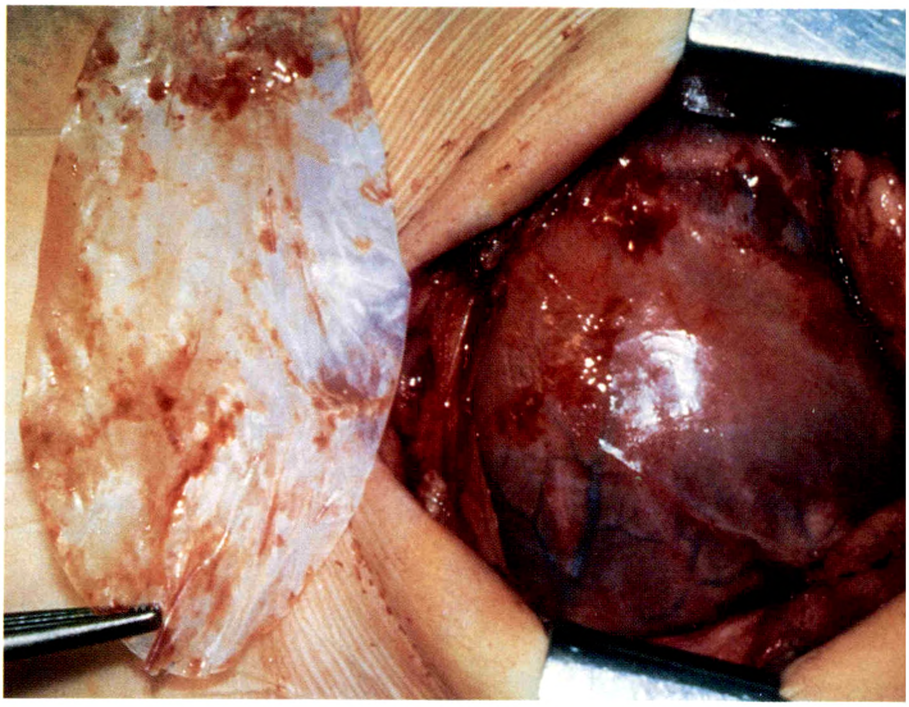

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The Department of Surgery at the Dartmouth-Hitchcock Medical Center, in Hanover, New Hampshire, is searching for an additional academic Cardiothoracic Surgeon at the Assistant/Associate Professor level. Candidates for this position must be BC/BQ in Thoracic Surgery and should have demonstrated, by prior training and experience, superior skills in all aspects of adult cardiac surgery as well as general thoracic surgery. The physician will be responsible for the care of patients in an established cardiothoracic practice at the Hitchcock Clinic with privileges extended to the Veterans Administration Hospital in White River Junction, Vermont.

The successful candidate should have demonstrated a commitment to research by previous experience and publications and will have the opportunity for further academic pursuits, including the education and training of medical students and house staff physicians. The individual will be an employee of the Hitchcock Clinic and will receive an appropriate academic appointment as a member of the faculty of Dartmouth Medical School. DHMC is an AA/EO employer and is especially interested in identifying female and minority candidates.

Inquiries and resumes should be directed to the Chair of the Search Committee: William C. Nugent, M.D., Chairman, Section of Cardiothoracic Surgery, Dartmouth-Hitchcock Medical Center, 2 Maynard Street, Hanover, NH 03756, (603) 646-7390.

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Contact:

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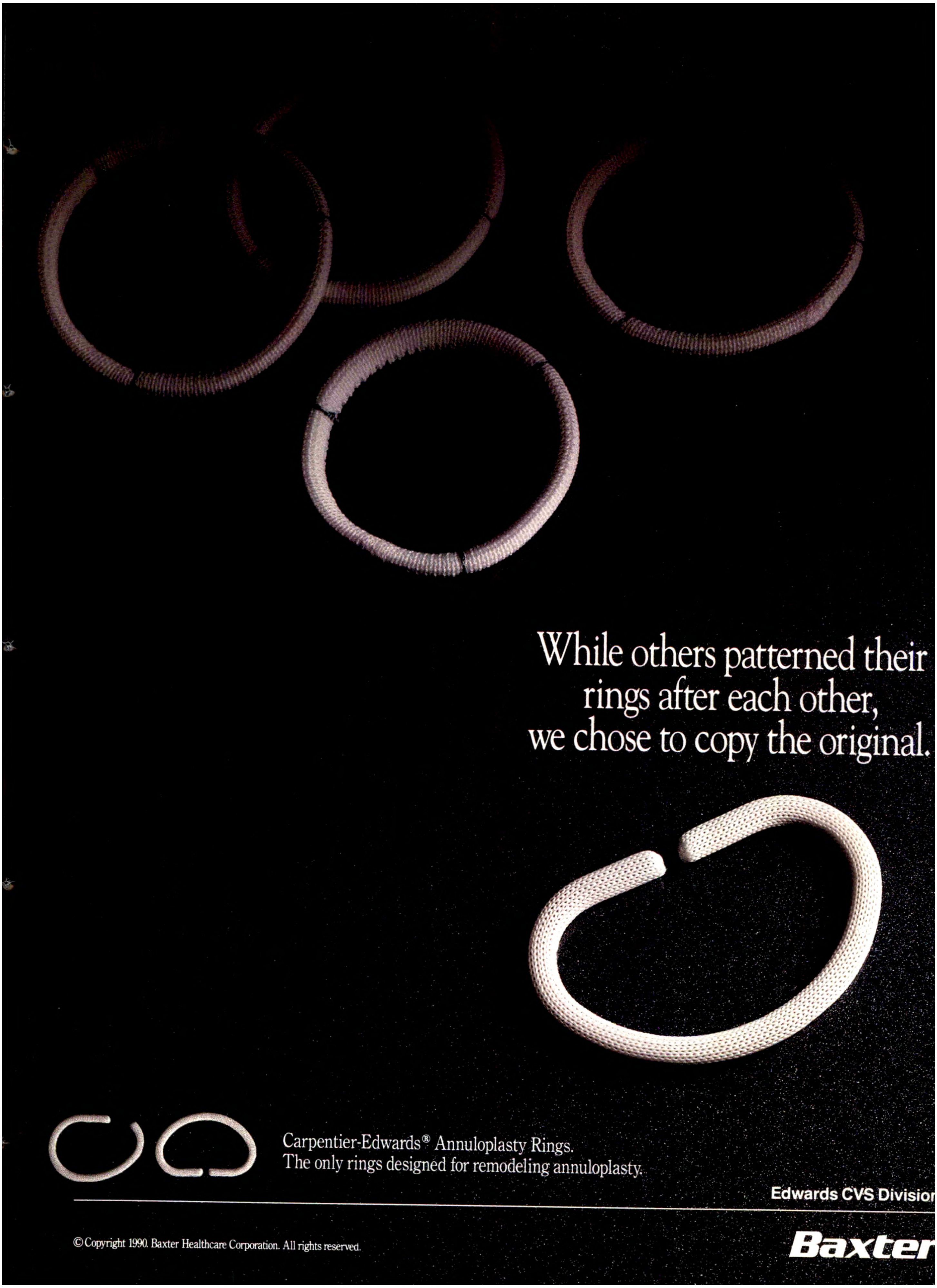

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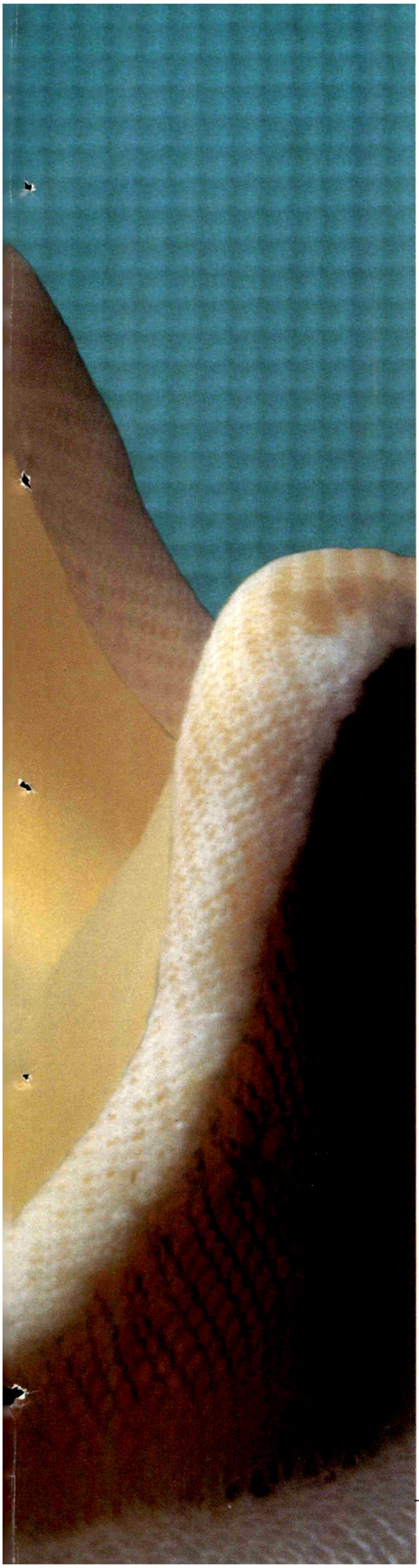

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The Carpentier-Edwards bioprosthesis is intended for use in patients whose aortic or mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted aortic or mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis. **Warnings:** For Single Patient Use Only In the presence of conditions affecting calcium metabolism or when calcium-containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, in the presence of severe systemic hypertension, and in patients who are on maintenance hemodialysis. The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient are made, and alternative methods of treatment are considered. Overall durability, especially long-term, has not been established for bioprostheses. Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery. **Note:** Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis. Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. The appropriate anticoagulation therapy must be determined by the physician on an individual basis. **Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result. The Carpentier-Edwards bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.** Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards bioprosthesis could damage the valve. Consequently, it is recommended that these procedures be avoided. Both the valve and glutaraldehyde storage solution are **sterile.** The outside of the jar is **not sterile** and must **not** be placed in the sterile field. Furthermore, the valve and container should **never** be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation. Storage between 10°C and 25°C is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue. **Any valve that has been frozen or exposed to temperatures greater than 60°C should not be used for human implantation.** Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with eyes, seek medical attention. **Surgical Precautions: 1.** When choosing a valve for a given patient, the size, age, and physical condition of the patient in relation to the size of the prosthesis must be taken into consideration to minimize the possibility of obtaining a suboptimal hemodynamic result. The selection of a valve, however, must ultimately be made by the physician on an individual basis after carefully weighing all of the risks and benefits to the patient. **2.** Due to the relative flexibility of the frame, care must be exercised to avoid the use of too large a prosthesis to prevent folding or extreme deformation of the stent that may render the valve incompetent. Oversizing may create highly localized mechanical stresses resulting in tissue failure in the form of detachment of the leaflets or porcine aortic wall from the valve stent posts. **3.** Left ventricular perforation or ulceration has been reported. Both open and closed chest cardiac massage in patients with an open strut mitral prosthesis increases the risk of ventricular perforation. Additionally, lifting, flexing, and manual compression of the distended heart after discontinuation of bypass may cause a commissure strut to be pushed through the endocardium, producing a dissecting hematoma with subsequent uncontrolled hemorrhage. **4.** The spacing of the sutures in the remnant of the valvular orifice and the prosthesis suture ring must be carefully matched to avoid folding of the leaflets or extreme distortion of the orifice. Edwards CVS Division has received reports in which individual mattress sutures, spanning a distance of 10 to 15mm, produced a purse-string effect causing compression of the valve orifice. **5.** When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue. Cases have been reported in which bioprostheses developed severe regurgitation and had to be replaced as a result of wear due to contact with sutures. **6.** Unlike rigid mechanical valves, the stent wall is soft and will not resist needle penetration. Accordingly, extreme care must be exercised when placing sutures through the sewing margin to avoid penetration of the side wall of the stent and possible laceration of the leaflet tissue. **7.** As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised, particularly in mitral replacement, to avoid looping or catching a suture around the free legs which would interfere with proper valvular function. **8.** The stent of the bioprosthesis is asymmetrical to conform to the natural shape of the porcine aortic valve. Consequently, the commissure supports are not equidistantly spaced. The contrasting suture markers in the sewing ring of the mitral valve denote the greatest intercommissural distance. These two commissure supports should be oriented so as to straddle the ventricular outflow tract to avoid murmurs due to blood flow turbulence. **Note:** The contrasting suture material should not be removed from the prosthesis. **9.** In the aortic position, the struts should correspond to the remnants of the natural commissures so as not to obstruct the coronary ostia. **10.** A serial number tag is attached to the sewing ring of each valve by a suture. This serial number should be checked against the number on the jar; if any difference is noted, the valve should be returned unused. This tag should not be detached from the valve until implant is imminent. Care should be exercised to avoid cutting or tearing the suture ring cloth during removal. **11.** Gentle handling is required for all implantable devices. If the valve is dropped, damaged, or mishandled in any way, it must not be used for human implantation. **Complications:** As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Complications associated with the use of Carpentier-Edwards bioprostheses include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct. **Note:** Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes an apparent causal relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards bioprostheses to calcification as compared to other commercially available porcine valves. **Caution:** Federal (USA) law restricts this device to sale by or on the order of a physician. Baxter International Inc. is the owner of the following US patent which covers the products described herein: 4,106,129. Patent numbers in foreign countries supplied upon request. See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information. Carpentier-Edwards® is a registered trademark of Baxter International Inc.

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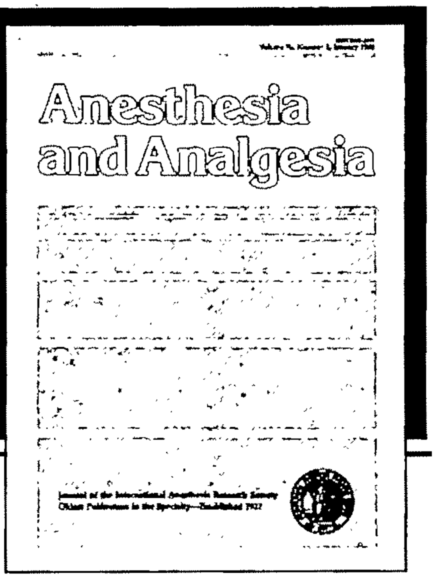

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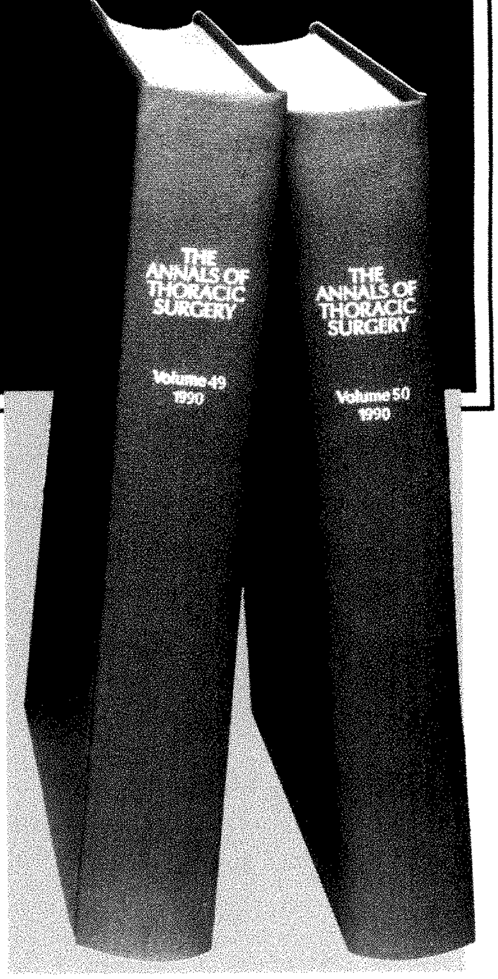
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Pneumonia After Coronary Artery Bypass Grafting: A Case for Continued Evaluation

Peter G. Tuteur, MD

Respiratory Diseases and Critical Care Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

What factors place those undergoing coronary artery bypass grafting (CABG) at increased risk for the development of postoperative nosocomial pneumonia? This is the question Gaynes and his colleagues address in their study reported in this issue [1]. Gaynes and associates find chronic obstructive pulmonary disease (COPD), duration of postoperative intubation and mechanical ventilation, and the administration of H_2 blockers all to be independent risk factors associated with post–CABG pneumonia. Unfortunately, direct application of this knowledge to clinical practice is impeded by the limitations inherent in the retrospective design of the study.

Gaynes and associates first searched for CABG patients on whom respiratory secretion cultures were obtained. Then they reviewed the medical records of those with positive cultures to assess who fulfilled criteria for the diagnosis of pneumonia. It should be noted that such a selection process might miss those cases in which cultures were not obtained, specimens were inadequate, or microbiological assessment was incomplete, ie, those not cultured for both bacteria and fungi. Furthermore, criteria for the diagnosis of the pneumonia required a positive radiographic evaluation in addition to culturing a pathogenic organism. Both the difficulties associated with interpretation of portable chest radiographs and the incompleteness of microbiological assessment may have led to an underestimate of the true number of pneumonia cases among the study cohort. This argument is consistent with the lower incidence and mortality rates observed by Gaynes and associates compared with those previously reported [2–4].

See also page 215.

Identifying COPD as an independent risk factor represents information difficult to apply in a clinical situation. One must ask, what were the criteria used for the COPD diagnosis? Were these criteria controlled among all physicians? Was the diagnosis made on history obtained at the time of admission to the hospital, detailed evaluation by a referring physician or consulting pulmonologist, and/or quantitative assessment of pulmonary function? Answers to these unaddressed questions may strengthen the opportunity for clinical application. The presence or absence of chronic sputum production, quantitative assessment of an obstructive ventilatory defect, and the character of preoperative outpatient and inpatient management may help to identify a subgroup of patients with COPD at even greater risk.

Another potential problem in interpreting these data lies in the database. Four of 19 medical records of "identified cases" were so incomplete that they had to be dropped from the analysis. Whether or not these unfound patients (21%) differed from the retained cohort it is unknown, but the potential for bias is serious.

Despite these limitations, the Gaynes study provides substantial insight to guide future investigation and clinical application. Based on these data and supported by the studies of Craven [4], Driks [5], and their co-workers it seems appropriate to select sucralfate to reduce the frequency of stress ulcer hemorrhage over the similarly effective H_2-blockers that are associated with higher incidence of nosocomial pneumonia. To further reduce the frequency of post–CABG pneumonia, one should evaluate factors that may influence poor outcome among some patients with COPD.

The literature is replete with studies identifying postoperative patients with COPD at risk not only for the development of pneumonia, but also for prolonged intubation [4, 6, 7]. Attempts to further identify a subgroup at even greater risk have met with mixed results. Some characteristics evaluated include: the quantitative assessment of severity of the obstructive ventilatory defect, the amount of daily mucus production, the use of preoperative therapeutic intervention in either the outpatient or inpatient setting, and assessment of efficacy of prophylactic postoperative therapeutic modalities [8, 9]. It also might be helpful to explore how aggressive pulmonary physiotherapy, prolonged intensive bronchodilator administration, patient education on cough training, use of incentive spirometry, and attention to adequate hydration influence outcome. The strategy of scheduling the at-risk patient with COPD as a "late case," permitting morning expectoration of chronically present respiratory secretions chronically present and recovery from the nadir of early morning pulmonary dysfunction, is a clinical approach used by some but never adequately evaluated.

Although the Gaynes study is not definitive, it does provide substantial information encouraging a future controlled prospective study designed to identify characteristics of patients with COPD at very high risk for post–CABG nosocomial pneumonia and to evaluate whether or not intervention can reduce this risk. It is not appropriate

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simply to discontinue use of H_2-blockers in this setting. To maximize the clinical utility of Gaynes and associates' observations, one also must address the other important questions raised by these preliminary data.

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Pulmonary Embolectomy

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Although Trendelenburg first suggested pulmonary embolectomy as early as 1908 [1], it remained for Kirschner, a pupil of Trendelenburg, to perform the first such operation associated with complete recovery in 1924 [2]. In the ensuing years many attempts to duplicate this heroic surgical feat almost universally met with failure. As late as 1961 only 23 reports of long-term survival after pulmonary embolectomy could be found in the world medical literature.

Successful pulmonary embolectomy using cardiopulmonary bypass first was reported in 1961 [3]. Since that time numerous similar successes have been reported, and it has become apparent that cardiopulmonary bypass not only allows resuscitation of the moribund patient with acute massive pulmonary embolism, but also provides sufficient time to adequately remove embolic material from the pulmonary arterial tree. Nevertheless, many have questioned the usefulness of this procedure, citing extremely high operative mortality rates. Most of these objections to pulmonary embolectomy have been based on the fact that many operations were performed on patients who did not have massive pulmonary embolism.

Others have assumed that the moribund patient with acute massive pulmonary embolism must live for at least an hour after pulmonary angiography for pulmonary embolectomy to be feasible. This argument is antiquated and fails to appreciate modern technological advances, including portable cardiopulmonary bypass equipment and the availability of organized surgical teams. Still others have stated that pulmonary embolectomy never is indicated.

See also page 232.

Nevertheless, a substantial number of patients continue to die of pulmonary embolism each year. It seems that the negative literature regarding surgical intervention has promoted a nihilistic attitude and currently many physicians never even consider the possibility of pulmonary embolectomy for the moribund patient. Occasionally, the subject is brought up at mortality and morbidity conferences after the patient has died. The inescapable conclusion is that, however infrequent, the opportunity to salvage an otherwise helpless situation is missed. Only with a high index of suspicion and a prearranged plan of approach to the dying patient with acute, massive pulmonary embolism can a substantial number of these patients be salvaged.

In this issue a 20-year experience with pulmonary embolectomy performed at one center in Paris is reported [4]. Ninety-six consecutive patients, of whom 92 had a definitive diagnosis by pulmonary angiography and 4 by perfusion lung scan, underwent pulmonary embolectomy with a salvage rate of 63%. The authors of this study conclude that most patients with pulmonary embolism can be treated by thrombolytic therapy and that pulmonary embolectomy only should be considered in hemodynamically compromised patients, in those in whom thrombolytic therapy is contraindicated, and in those so severely affected that the time required by an attempt at medical therapy is thought to be unacceptable.

These conclusions are valid and are supported by their data and others. Most patients with pulmonary embolism can be treated medically with only the occasional patient requiring pulmonary embolectomy for survival. In this small group of moribund patients with massive pulmonary embolism, however, the most likely outcome would be death in virtually all without operation.

Even after cardiac arrest the patient with massive pulmonary embolism often can be resuscitated by femoral vein to femoral artery cardiopulmonary bypass, thus providing oxygenated blood to such vital areas as the heart, brain, and kidneys [5]. With currently available portable pump oxygenators such a patient then can undergo pulmonary angiography for definitive diagnosis [6]. Finally, only those shown to have massive pulmonary embolism would be taken to the operating room for pulmonary embolectomy. With such an approach salvage rates for the few patients needing this procedure can be sizable. It is illogical to abandon a therapeutic modality that has the ability to correct a lethal mechanical problem in an otherwise salvageable patient.

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Retrograde Continuous Warm Blood Cardioplegia

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The concept of retrograde continuous warm blood cardioplegia is truly a different approach to myocardial preservation deserving of our consideration. In analyzing the pros and cons of this methodology, it is first appropriate to discuss the retrograde route of cardioplegic administration, which has in recent years become increasingly popular. Coronary sinus cardioplegia is an approach based largely on an understanding of coronary venous and arterial anatomy. This was reviewed in some detail by Hochberg and Austen in 1980 [1]. Their analysis explains quite simply how the coronary venous drainage patterns can be divided into two systems: the "greater system" incorporates the myocardial arterioles draining into capillaries and subsequently into the coronary venous system, emptying into the great and middle veins, the coronary sinus and right atrium. Approximately 73% of venous drainage in the heart occurs through this system. Hochberg and Austen [1] have also defined a "lesser system" that drains approximately 27% of the coronary arterial blood through a deep venous circulation that drains directly into the cardiac chambers. These have been termed the arteriosinusoidal and thebesian vessels. Thebesian channels drain into the right ventricle whereas the arteriosinusoidal vessels drain primarily into the left ventricle. Thus, in an antegrade direction, approximately 27% of coronary arterial blood bypasses the normal venous drainage system and enters the ventricular chambers directly through either thebesian or arteriosinusoidal channels.

See also page 245.

Partington and associates [2] have more recently reported on microsphere studies that clearly define how retrograde perfusion at 50 mm Hg of blood cardioplegia through the coronary sinus distributes into myocardial tissue in regions of both open and occluded coronary arteries. These authors reported that in the arrested heart, total cardiac nutritive retrograde flow averaged 70% (± 4%) of the delivered flow when the coronary arteries were patent and fell to 61% (± 6%) when the left anterior descending artery was occluded. Conversely, they found that 30% (± 4%) and 39% (± 6%) of the injected microspheres bypassed the myocardial capillary bed with all vessels open and the left anterior descending artery occluded. The only criticism that can be leveled against this very carefully performed study relates to the fact that it was done in dogs, and there are undoubtedly species differences in coronary venous anatomy. One is clearly struck by the correlation between the 73% figure for the greater venous drainage system as described by Hochberg and Austen [1] and the 70% nutritive retrograde perfusion as described by Partington and co-workers in the arrested canine heart [2]. One must remember that there is a natural advantage of retrograde cardioplegia in its ability to bypass obstructed coronary arteries, providing distal myocardial preservation.

A concern about retrograde preservation deals with the possibility of inadequate preservation of the right ventricle, a subject well discussed by Menasché and associates [3]. In their report, pathological studies, presumably in humans, have shown that veins draining the right ventricle and posterior part of the interventricular septum can drain into the more distal portion of the coronary sinus, as close as 0.5 cm from its termination in the right atrium, and thus be subject to occlusion by a balloon placed within the coronary sinus, preventing retrograde perfusion of these venous channels. This is consistent with the findings reported by Partington and associates [2] employing a coronary sinus indwelling balloon, where the lowest retrograde coronary sinus nutritive flow always occurred in the right ventricular free wall with measured flows of 7 ± 2 $\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$ compared with 82 ± 11 $\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$ in the anterior left ventricular free wall under comparable conditions. Additionally, retrograde flow to the interventricular septum was measured at 23 ± 9 $\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$, a figure again considerably lower than that to the left ventricular free wall. Thus, it is likely that flow to the septum and right ventricle may be deficient by the retrograde approach. It is of critical importance in examining the use of retrograde continuous warm blood cardioplegia to consider how much blood is actually necessary in the arrested, perfused, warm myocardium to sustain myocardial metabolic demands.

Details on myocardial oxygen consumption in the arrested, normothermic and hypothermic heart have been definitively studied in Buckberg's laboratory [4]. Myocardial oxygen consumption in the beating, empty left ventricle at 37°C is 5.6 $\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$, but in the arrested left ventricle it is only 1.1 $\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$, a decrease of more than 80%. As the temperature falls, the level of oxygen demand decreases dramatically to 0.3 $\text{mL} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$ at 22°C [4] with presumably a continued decrease as myocardial temperature approaches 10°C, a temperature that is frequently reached during hypothermic cardioplegic arrest. It is thus appropriate to enumerate briefly the advantages or disadvantages of hypothermic versus normothermic preservation. Easily, the major consideration in cooling the arrested heart

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relates to the oxygen needs of the hypothermic versus the normothermic myocardium. If one is to supply nutrient to the ischemic heart periodically during arrest, clearly having a lower oxygen demand would be preferable. Using continuous retrograde cardioplegia clearly voids this argument as sufficient myocardial metabolic demands can be easily achieved with oxygenated warm blood with O_2 contents in excess of 15 mL O_2/100 mL blood.

An obvious question that should be raised deals with why not to employ hypothermia. There are two issues to be addressed. First, is myocardial hypothermia induced by blood cardioplegia at 10°C inherently deleterious? Standeven and associates [5] addressed this issue using microsphere distribution and found no alteration in endocardial/epicardial flow ratios with blood cardioplegia at 6°C. They felt that this supported the conclusion that there was no significant alteration in blood viscosity, rouleaux formation, or sludging at these lower temperatures. Magovern and co-workers [6] studied the efficacy of blood cardioplegia to preserve myocardial function when administered at 20°, 10°, and 4°C. Although they did not measure blood flow distribution or document sludging of red blood cells at 4°C, they clearly showed that functional recovery was significantly improved at the warmer blood cardioplegic temperature (20°C) associated with significantly better oxygen delivery. The investigators measured myocardial oxygen tension by mass spectrometry and were able to show that oxygenated blood cardioplegia only at 20°C significantly increased myocardial oxygen tension. Left ventricular myocardial oxygen consumption was significantly greater with blood cardioplegia at 20°C than at either 10° or 4°C. It is presumed by Magovern and co-workers [6] that the decreased oxygen delivery at the lower temperature is related to the naturally occurring shift to the left of the oxygen dissociation curve with decreasing blood temperature. It is this work which has contributed to the experimental support for the use of oxygenated cold crystalloid cardioplegia with maintenance of myocardial temperatures between 10° and 15°C.

The issue of systemic hypothermia versus normothermia cannot adequately be addressed in this editorial. Salerno and co-workers [7] have provided a number of references that deal with the potentially deleterious effects of hypothermia on multiple organ systems. Clearly, hypothermia to levels of 20°C perfusion temperature affects the conduct of cardiopulmonary bypass, requiring systemic rewarming and promoting defects in variables of coagulation that are now being studied [8].

Finally, there are those of us who have employed warm retrograde cardioplegia clinically and looked at it critically to attempt to define its role. First, continuous cardioplegia is not necessary. The administration of the retrograde infusion can be stopped periodically for construction of coronary arterial anastomoses, dissection on the heart, or implantation of a valve if the appearance of blood prevents accurate suture placement. There is no clear knowledge as to how long the infusion can safely be interrupted. Second, the question of distribution of retrograde infusion is always of concern, and there is no way at present to know that cardioplegia is being adequately distributed. Future approaches may well solve this dilemma, such as the use of pH or oxygen probes, but at the moment nothing is commercially available to allay a surgeon's anxieties. In fact, the two issues of adequate distribution and how long to interrupt infusion are interrelated in the critical question of whether nutritive flow is reaching all of the myocardium and thus preventing ischemic injury. Salerno and co-workers [7] have deliberately maintained cardioplegic perfusion pressures in the coronary sinus below 40 mm Hg and indicate how this correlates with relatively low flow (mean of 122 mL/min), which is undoubtedly sufficient to maintain oxygen and nutrient supply. The issue as to whether some of this administered blood should be infused through each completed vein graft during coronary revascularization was not addressed in this article, but this is an approach that is commonly performed in addition to maintaining coronary sinus retroperfusion.

The patients in whom we have used this technique have had their electrocardiogram return to baseline and forceful, nonischemic contractility result soon after resumption of normal antegrade flow with removal of aortic occlusion. However, in patients with massive left ventricular hypertrophy (eg, aortic stenosis), the impossibility of assuring adequate distribution of retrograde flow and thus assuring yourself of the adequacy of preservation at normothermia has forestalled acceptance of this approach.

Given all of the above considerations, retrograde continuous warm blood cardioplegia is extremely useful and certainly applicable for the majority of adult patients.

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Chest Wall Involvement by Lung Cancer: Computed Tomographic Detection and Results of Operation

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The aim of this prospective study was to evaluate: (1) the role of computed tomographic scanning in predicting chest wall invasion by peripheral lung cancer and (2) the results of operation according to the depth of chest wall involvement and other potential indicators of long-term survival. One hundred twelve patients with non–small cell lung cancer adjacent to the pleural surface who underwent computed tomographic scanning and subsequent thoracotomy were entered into this study. Tumor invasion was confined to the visceral pleura in 53 patients, to the parietal pleura in 18 patients, and to intercostal muscles in 25 patients; invasion extended beyond this layer in 16 patients. The computed tomographic criteria for chest wall invasion were (1) obliteration of the extrapleural fat plane, (2) the length of the tumor-pleura contact, (3) the ratio between the tumor-pleura contact and the tumor diameter, (4) the angle of the tumor with the pleura, (5) a mass involving the chest wall, and (6) rib destruction. The computed tomographic criteria 1 and 3 were significantly related to pathologic findings. Sensitivity was 85% for criterion 1 and 83% for criterion 3, specificity being 87% and 80%, respectively. Long-term survival of patients with T3 disease critically depended on the lymph node state and completeness of resection. The adenocarcinoma cell type and the T4 category were unfavorable prognostic factors. The depth of chest wall invasion did not affect survival, except for extensive rib and soft tissue infiltration. En bloc resection yielded better results than discontinuous resection.

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Surgeons have now recognized that patients with non–small cell lung cancer invading the chest wall have a potential long-term survival, provided that complete resection is feasible and mediastinal node involvement is not present [1–3]. The decision whether to undertake en bloc resection of the lung and chest wall or to attempt extrapleural dissection depends on the presumed degree of peripheral tumor spread. Even intraoperatively, differentiation between neoplasms confined within the parietal pleura from those infiltrating the chest wall proper may be difficult. Preoperative assessment of chest wall involvement is therefore important in planning treatment. Although computed tomographic (CT) scanning has been suggested to be less than adequate to establish the depth of chest wall infiltration [4–6], it remains the most accurate diagnostic procedure currently available in Italy.

The present prospective study was carried out to evaluate (1) the diagnostic accuracy of individual CT criteria and their combinations in predicting the extent of chest wall invasion and (2) the results of operation according to the depth of chest wall involvement and other potential indicators of long-term success.

Patients and Methods

From January 1983 through December 1988, patients admitted to four institutions (Clinica Chirurgica Ia, University of Genoa; San Martino and Sanpierdarena Hospitals, Genoa; and Alessandria Hospital, Alessandria) with peripheral, potentially resectable lung cancer were entered into this prospective study. The inclusion criteria were (1) histologic diagnosis of non–small cell lung cancer, (2) preoperative CT scanning demonstrating contiguity of the tumor with the pleural surface, and (3) thoracotomy performed. Subjects who had superior sulcus neoplasms, malignant pleural effusions, or preoperative radiotherapy and those who were not available to follow-up were excluded from the study. Computed tomographic images were read independently by two of us (C.F. and F.M.) before operation. They were asked if the tumor was confined within the parietal pleura or invaded extrapleural soft tissues. Preoperative staging procedures included chest roentgenography, bronchoscopy, and computed tomography of the chest and abdomen. Bone and brain scans, as well as cervical mediastinoscopy, were not included in the staging protocol. Throughout the entire study duration, the follow-up of patients was carried out according to Ginsberg's suggestions [7].

There were 102 men and 10 women. The mean age was 59.8 ± 8.6 years. Histology of the primary tumor was squamous cell carcinoma (47 patients), adenocarcinoma (56), large cell carcinoma (5), and adenosquamous carci-

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noma (4). At operation, 13 neoplasms proved to be unresectable because of invasion of the spine, unremovable node metastases, or aortic arch infiltration. In 13 patients the resection was classified as incomplete because microscopic examination showed either the margins of the resected specimen or the most distally removed node in major lymphatic drainage regions to be infiltrated by tumor cells. Of the 86 subjects who underwent a complete resection, 21 had pneumonectomy and 65 lobectomy or bilobectomy. Biopsies of attainable paratracheal, subcarinal, inferior pulmonary ligament, and hilar nodes were routinely performed.

The same surgical policy was applied by the surgeons participating in the study (G.B.R., I.S., R.G., and P.J.). The decision to perform an extrapleural dissection or en bloc resection depended on the operative findings. A trial of extrapleural dissection was attempted when there was no clear evidence of tumor extension into the intercostal muscles or ribs. This approach was used in 76 patients: 18 had parietal pleura invasion and 19 had tumor extension beyond the parietal pleura. In these latter patients, the involved chest wall was discontinuously resected. If during extrapleural dissection there was strong fixation of the parietal pleura to the overlying ribs, en bloc resection was carried out (18 patients). The number of resected ribs ranged from one to four. Prosthetic materials were never used for parietal reconstruction.

Nineteen neoplasms were postsurgically classified as stage I, 9 as stage II, 66 as stage IIIa, and 18 as stage IIIb. Histologic examination of the removed specimens demonstrated tumor involvement confined to the visceral pleura in 53 patients, parietal pleura involvement in 18, and intercostal muscle or rib periostium involvement in 25. In 16 patients there was either soft tissue infiltration beyond the intercostal muscles or rib destruction. Postoperative radiation therapy was given to patients with known residual tumor. Two patients died within 30 days after operation because of respiratory failure and intrathoracic bleeding. No death followed en bloc or discontinuous chest wall resection.

Computed Tomographic Investigations

Computed tomographic scans of the chest were obtained using a Somatom II (Siemens, Erlangen, Germany) scanner. Contiguous cuts, 8 mm thick, were taken at full inspiration from the diaphragm to the lung apexes without overlap. Contrast medium was infused intravenously. The CT scanning criteria used to predict the depth of chest wall involvement were (1) obliteration of the extrapleural fat plane, (2) the length of the tumor contact with the adjacent pleural surface, (3) the ratio between the amount of tumor-pleura contact and the tumor diameter, (4) the angle of the tumor with the pleura (acute or obtuse angle), (5) an obvious mass extending into the chest wall soft tissues, and (6) rib destruction. Thickening of the pleura adjacent to the neoplasm was not taken into account because it has been previously demonstrated to be nonspecific [4]. The extrapleural fat plane was not uniformly discernable, particularly on CT cuts corresponding to the rib level. Nevertheless, the plane was practically always visible if researched between the pleura adjacent to the tumor (which was often thickened) and the intercostal muscle layer (Fig 1). Measurement of tumor diameter was obtained from CT scans using the soft-tissue window settings [4]. Differentiation between cancer and surrounding atelectasis or pneumonitis was attempted by analyzing the vascularization patterns after contrast medium injection. The contact between abnormal lung and chest wall was assessed as shown in Figure 2. Rib destruction was searched for using the thin-cut technique and was defined as any evidence of irregular rib contour (see Fig 1). When the angle of the tumor with the pleura was either acute or obtuse in different areas, it was classified as obtuse.

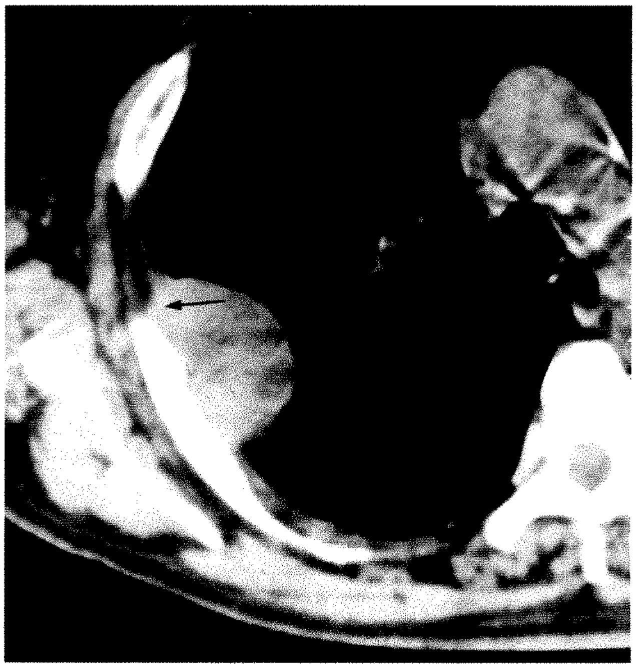

Fig 1. Right bronchogenic carcinoma contiguous with the chest wall. The extrapleural fat plane is well visible, with the arrow *showing encroachment of tumor on extrapleural fat. Irregularity of the rib border, suggesting bone erosion, is also demonstrated.*

Statistical Analysis

Computed tomographic findings were correlated with pathologic findings, which were assumed as the true reference. Comparison was made in terms of sensitivity, specificity, and accuracy according to standard formulas. The predictive value of CT results was assessed both for each CT criterion and for their combinations. When a combination of several CT criteria was used, the diagnostic efficacy of the test was evaluated in two ways: (1) by classifying the test positive if at least one CT criterion indicated tumor infiltration beyond the parietal pleura, and (2) by considering the test positive if all the selected CT criteria suggested chest wall invasion. The strength of the association between the results provided by CT scanning and by thoracotomy was evaluated by multiple regression analysis. Because CT criteria 1, 5, and 6 were

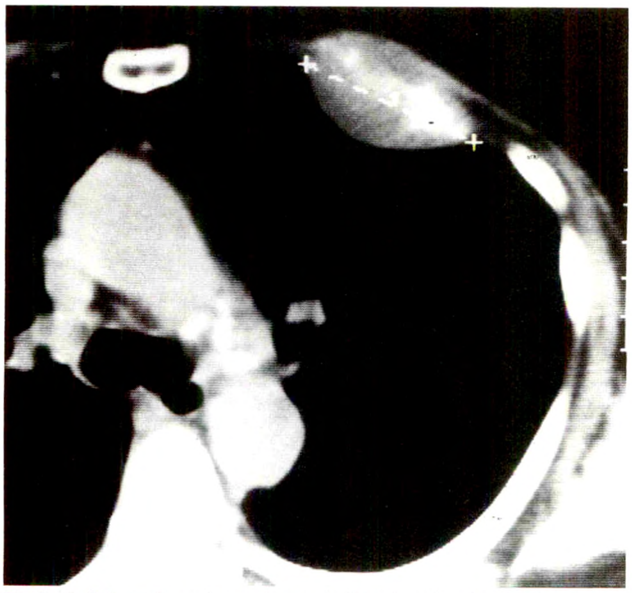

Fig 2. Left bronchogenic carcinoma infiltrating the chest wall. The technique used for measuring the length of tumor in contact with pleura is illustrated.

subjective in nature, intraobserver and interobserver variation have been estimated by means of the ϕ coefficient method. This coefficient was 0.03 for intraobserver variation and 0.05 for interobserver variation. Survival rates have been calculated by the Kaplan-Meier method. Comparison of survival curves was done by the Mantel-Haensel test.

Results

Sensitivity, specificity, and accuracy of individual CT criteria for the diagnosis of chest wall invasion, as well as the predictive value of positive or negative tests, are reported in Table 1. Sensitivity, specificity, and accuracy rates of CT criterion 2 (the length of the tumor contact with the adjacent pleural surface) when using different cut-off values separating patients with chest wall infiltration from those without infiltration are listed in Table 2. Sensitivity, specificity, and accuracy rates of CT criterion 3 (the ratio between the length of tumor-pleura contact and the tumor diameter) when adopting various cut-off values are summarized in Table 3. The correlation between CT data and pathologic findings was significant for CT criteria 1 ($p < 0.001$) and 3 ($p < 0.01$). Sensitivity, specificity, and accuracy rates of combining CT criteria 1 and 3 are shown in Table 4.

The patients' age and sex, the tumor diameter, and the number of resected ribs did not significantly affect survival. Survival rates depended on the tumor stage ($p < 0.05$) and histology ($p < 0.05$), the length of tumor-pleura contact ($p < 0.05$), and the completeness of resection ($p < 0.001$). The 5-year survival rate, according to the disease stage, was 48% in stage I, 31% in stage II, 12% in stage IIIa, and 0% in stage IIIb. Survival curves of patients with T3 tumors, according to the N status, are illustrated in Figure 3. Patients with cancers classified as T3 N0 survived longer than those with cancers classified as T3 N2 ($p < 0.05$); patients with T3 N1 lesions also survived longer than those with T3 N2 lesions ($p < 0.05$). Similar conclusions were obtained when the analysis was restricted to the individuals who had undergone a complete resection. The 5-year survival rate, according to the tumor cell type, was 25% in subjects with squamous cell carcinoma and

Table 1. Computed Tomographic Scan Criteria for Chest Wall Invasion

Value	Obliteration of the Extrapleural Fat Plane	Obtuse Angle	Chest Wall Mass	Rib Destruction
Sensitivity (%)	85	57	33	16
Specificity (%)	87	72	100	98
Accuracy (%)	86	66	75	67
Positive predictive value (%)	80	55	100	87
Negative predictive value (%)	91	73	71	66

Table 2. Diagnostic Efficacy of Computed Tomographic Criterion 2 (Length of Tumor Contact With Pleural Surface) According to Different Cut-off Values for Separating Patients With Chest Wall Invasion From Those Without

	Tumor-Pleura Contact (cm)		
Value	3	4	5
Sensitivity (%)	97	92	76
Specificity (%)	42	54	68
Accuracy (%)	61	67	71
Positive predictive value (%)	51	54	59
Negative predictive value (%)	97	93	83

Table 3. Diagnostic Efficacy of Computed Tomographic Criterion 3 (Ratio Between Tumor-Pleura Contact and Tumor Diameter) According to Different Cut-off Values for Separating Patients With Chest Wall Invasion From Those Without

	Tumor-Pleura Contact/Tumor Diameter		
Value	0.5	0.7	0.9
Sensitivity (%)	100	92	83
Specificity (%)	37	62	80
Accuracy (%)	60	74	81
Positive predictive value (%)	48	60	71
Negative predictive value (%)	100	94	89

Table 4. Combined Use of Computed Tomographic Criteria 1 and 3 (Adopting 0.7 as Cut-off Value) for Predicting Chest Wall Invasion

Value	A	B
Sensitivity (%)	97	81
Specificity (%)	61	89
Accuracy (%)	75	86
Positive predictive value (%)	60	81
Negative predictive value (%)	98	89

A = test classified as positive if at least one criterion indicates chest wall invasion; B = test classified as positive if both criteria indicate chest wall invasion.

17% in those with adenocarcinoma. When limiting the study to patients who had a potentially complete resection, the relevant figures were 30% and 19%, respectively. The length of the tumor-pleura contact affected survival exclusively when lesions adhering less than 3 cm were compared with lesions adhering more than 6 cm (either if considering the entire series or just the completely resected cases). The 5-year survival rate of patients with T3 tumors who underwent a complete resection (45 patients) was 16%. There were no 2-year survivors in the group of patients with T3 tumors who had incomplete resection or no resection (10 patients).

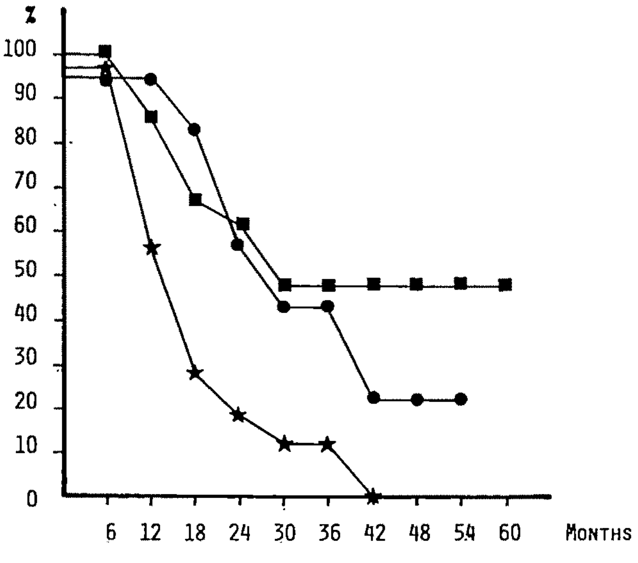

Fig 3. Survival curves of patients with tumors extending to or beyond the parietal pleura (T3 tumors), according to the N status. (■——■ T3 N0, 14 patients; ●——● T3 N1, 19 patients; ★——★ T3 N2, 22 patients.)

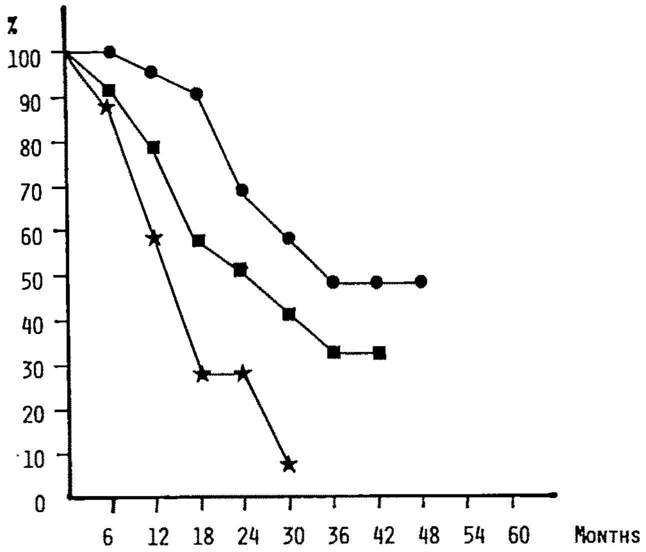

Fig 4. Survival curves of patients with tumors extending to or beyond the parietal pleura, according to the type of resection. (■——■ extrapleural dissection, 18 patients; ●——● en bloc resection, 18 patients; ★——★ discontinuous resection, 19 patients.)

Survival rates of patients with tumors extending to or beyond the parietal pleura who had undergone an extrapleural dissection, en bloc resection, or discontinuous resection of the involved lung and chest wall are shown in Figure 4. There was no significant difference in survival between patients of the extrapleural dissection group and those of the en bloc resection group. Survival rates after a discontinuous resection were significantly poorer than those after en bloc resection ($p < 0.01$). Survival rates according to the depth of chest wall infiltration are illustrated in Figure 5. The probability of long-term survival for patients with cancers confined to the visceral pleura was significantly greater than that of patients with rib destruction or soft tissue infiltration beyond the intercos-

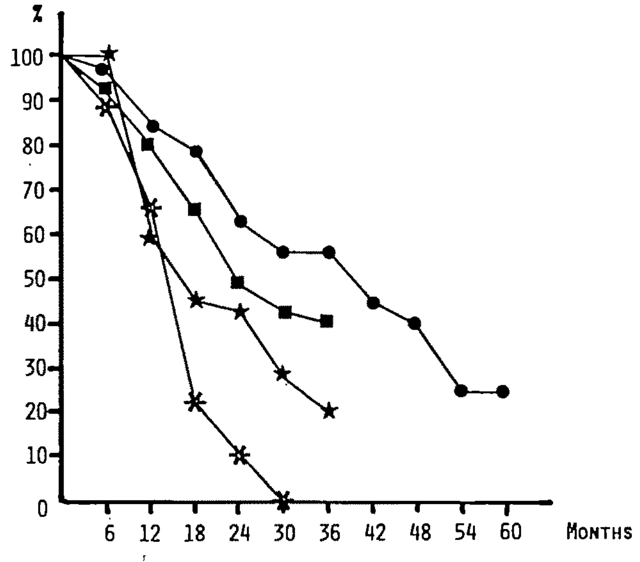

Fig 5. Survival curves of patients with tumors contiguous with the pleural surface, according to the depth of chest wall infiltration. (●——● tumor involvement confined within the visceral pleura, 53 patients; ■——■ parietal pleural involvement, 18 patients; ★——★ intercostal muscle or rib periostial involvement, 25 patients; ✳——✳ rib destruction or chest wall infiltration beyond intercostal muscles, 16 patients.)

tal muscles ($p < 0.01$ for the entire series; $p < 0.05$ for completely resected cases). No significant difference in survival was found among patient groups with intermediate degrees of chest wall infiltration.

Comment

Preoperative diagnosis of chest wall invasion by primary lung cancer is important for surgical strategy. Mortality and morbidity associated with unnecessary extended resections [8–10] or unneeded violations of the tumor plane could be avoided. Combined therapy programs, including the use of preoperative radiotherapy, might be prospectively applied. Patients with chest wall invasion and mediastinal node metastases, who do not seem to benefit from en bloc resection [8, 10, 11], could be excluded from radical operations.

Although CT scanning has been recognized as a more accurate diagnostic procedure than standard tomography [12–15], it has been recently suggested to be unsuitable to differentiate tumor contiguity with the pleural surface from definite chest wall invasion [4–6, 16]. The individual criteria used to predict chest wall infiltration proved to be either highly sensitive but nonspecific or highly specific but insensitive. Among the criteria adopted in the present study, obliteration of the extrapleural fat plane was the most significantly related to pathologic findings. Both sensitivity (85%) and specificity (87%) rates were acceptable. The major criticism to the use of this criterion is the variable thickness of the extrapleural fat plane, often indistinguishable on CT images. In our experience, the fat plane between the pleura adjacent to or invaded by the tumor and the intercostal muscle layer was virtually always visible. One could object that, by focusing the analysis to the intercostal muscle regions, rib invasion without obvious bone destruction might have been overlooked. Actually, this occurred in 3 patients only, suggesting that the event is not common. Whether radionuclide bone scanning could be useful in identifying patients with rib involvement undetectable on CT scans remains to be clarified. A false diagnosis of extrapleural fat plane obliteration was made in 9 patients. According to Pennes and associates [4] and Shin and co-workers [17], the relevant causes have been identified in concomitant inflammatory processes of the pleura extending into the extrapleural fat or in chest asymmetry due to the patient's position.

Besides obliteration of the extrapleural fat plane, the only CT criterion significantly related to pathologic data was the ratio between the tumor-pleura contact and tumor diameter. One of the reasons accounting for this finding might reside in the fact that measurement errors were in part withdrawn by expressing the final results as a ratio. If surrounding atelectasis or pneumonitis would be erroneously deemed cancer, inaccuracy might affect the size of both the tumor diameter and tumor-pleura contact. All the remaining CT criteria that have been used in this study were not significantly associated with pathologic data. In an attempt to enhance the predictive value of CT findings, we combined the results of criteria 1 and 3. By using such an association, the following information could be obtained: (1) if both criteria are negative, the surgeon may be almost certain that an extrapleural dissection will not violate the cancer plane (sensitivity: 97%); (2) if both criteria suggest chest wall invasion, the surgeon will be advised against extrapleural dissection (specificity: 89%).

The relationship between the depth of chest wall infiltration and prognosis is one of the still-unsolved problems. Gronqvist and associates [18] and Mishina and colleagues [19] suggested that invasion of the pleura is a more favorable indicator than invasion of intercostal muscles, whereas rib involvement gives the worst prognosis. Neef [20] and Martini [21] claimed that patients with invasion of the chest wall proper have a poorer prognosis than patients with invasion of the parietal pleura only. By contrast, McCaughan and co-workers [1] found that the extent of chest wall involvement does not significantly affect survival. The present study showed that tumor infiltration confined within the visceral pleura is significantly associated with a better outcome if compared with infiltration of chest wall soft tissues beyond the intercostal muscles or rib destruction. No significant difference in survival was demonstrated between patients with parietal pleura involvement and those with involvement of the chest wall proper. The observation remained valid even when corrected for the completeness of resection and nodal metastases. However, it should be noted that patients with parietal pleura invasion or chest wall invasion were unevenly treated. The chosen operation in subjects with tumor growth confined to the parietal pleura was extrapleural dissection, whereas subjects with invasion beyond the parietal pleura underwent en bloc or discontinuous chest wall resection.

Controversy continues concerning the value of potential indicators of long-term success in patients with lung cancer abutting the chest wall [1, 2, 11, 22]. In accordance with previous reports [1, 10, 11, 19], the present study confirmed that long-term survival is highly dependent on the lymph node state and completeness of operation. The poor results we have obtained in patients with T3 N2 disease further stress the need for mediastinoscopic exploration in individuals whose CT scanning shows chest wall infiltration and enlarged mediastinal nodes [11]. The lack, in our experience, of 2-year survivors after incomplete resection and radiotherapy does not support the efficacy of combining these therapeutic modalities.

The other prognostic factors we found to be correlated with long-term survival were tumor histology, the T component, and the type of resection. Patients with squamous cell carcinoma had a better outcome than those with adenocarcinoma. This finding might suggest that the diagnostic approach to patients with adenocarcinoma invading the chest wall should include a meticulous search for distant metastases to determine if they are actually M0. The erosion of survival expectation according to the T categories was significantly higher for T4 tumors than for T2 or T3 tumors. This would indicate that patients with vertebral body or great vessel invasion are poor candidates for surgical resection [2].

The prognostic value of the type of resection has been differently appreciated by authors. Grillo [11] found 3 long-term survivors in a group of 19 patients who had undergone en bloc resection, and none in a group of 14 patients in whom extrapleural dissection of a tumor involving the parietal pleura was done. Trastek and associates [23], analyzing subjects with lung cancer infiltrating the parietal pleura, noted 5-year survival rates of 75% after en bloc resection and 27.9% after extrapleural dissection. McCaughan and colleagues [1] only attempted en bloc resection when there was operative evidence of intercostal muscle or rib invasion, and they concluded that survival is superior in patients undergoing extrapleural dissection (48%) than in those who had en bloc resection (16%). Casillas and co-workers [24] reported no significant difference in survival between the en bloc resection (21% at 5 years) and the extrapleural dissection (24%) groups. In the present series, the survival rates of patients who underwent en bloc resection were not statistically different from those of patients who underwent extrapleural dissection. Nevertheless, there was a tendency toward a better outcome in the first group than in the second group. This in spite of the more extended chest wall invasion characterizing subjects who required en bloc resection. We found survival to be significantly impaired when a discontinuous resection was carried out in place of en bloc resection. This observation is at variance with a previous report [10] suggesting that discontinuous resection may be adequate in patients with tumor extension beyond the parietal pleura. The explanation might be that, in the earlier series, discontinuous resection was applied only when the adherence of the lung to the chest wall was neither solid nor extensive, whereas this was not always true in the present series.

In conclusion, among the numerous CT criteria used for preoperative assessment of chest wall invasion by primary non–small cell lung cancer, obliteration of the extrapleural fat plane and the tumor-pleura contact-tumor diameter ratio were the only variables significantly related to pathologic findings. The depth of chest wall infiltration did not affect long-term survival, provided that extensive invasion of chest wall muscles or ribs was not present. Survival was critically dependent on the lymph node state and completeness of resection. The adenocarcinoma cell type and the T4 category were unfavorable prognostic factors. In patients with tumors extending beyond the parietal pleura, en bloc resection yielded better success rates than discontinuous chest wall resection. Whether en bloc resection is more advantageous than extrapleural dissection in patients with neoplasms confined to the parietal pleura needs further investigation.

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Esophageal Malignancies: Is Preoperative Radiotherapy the Way to Go?

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During the period 1969 to 1988, 68 patients with esophageal malignancy were subjected to preoperative radiotherapy consisting of 30 Gy over 3 weeks followed by esophagectomy after a wait of 2 weeks. Sixty-two of 68 patients (91%) were followed up retrospectively (5-year survival rate, 17.2%; 10-year survival rate, 4.8%). Radiosensitivity of the tumor was graded by a radiation effect scoring method devised by us, and this was found to correlate with long-term prognosis ($p = 0.05$). Radiotherapy "sterilized" malignant involvement of adventitia and draining lymph nodes in 8 patients and thereby converted "palliative" into potentially "curative" resections with a mean survival of 57.2 months in this group of patients. Preoperative radiotherapy was found to increase the survival, decrease the incidence of residual tumor at the resected stump, reduce the incidence of local recurrence, and increase the resectability rate.

(Ann Thorac Surg 1991;51:189–93)

Despite advances in the surgical and ancillary services involved in the treatment of esophageal malignancies, this cancer continues to remain a formidable challenge to the surgeon. The grave and dismal long-term prognosis with operation alone prompted the introduction of adjuvant therapy. Taking the lead from Nakayama and associates [1], the Cardiothoracic Unit at Royal Perth Hospital has used preoperative radiotherapy as an adjuvant to operation since 1969. This study reviews our experience with this method of management of esophageal malignancy.

Material and Methods

The unit operated on 68 patients during the period 1969 to 1988. All patients, irrespective of the location and nature of the malignant lesion, were subjected to preoperative radiotherapy consisting of 30 Gy over 3 weeks (2 Gy per day, 5 days per week) using a deep-ray cobalt unit followed by an operation 2 weeks later. Classic Ivor-Lewis esophagectomy consisting of laparotomy and a right thoracotomy was performed in 57 patients, esophagectomy through the left thoracoabdominal approach in 8, and blunt esophagectomy in 3. Stomach was used as esophageal substitute in all but 1 patient, in whom colon was used, and fundal wrap and pyloroplasty were done routinely. All anastomoses were hand sewn. The patients were followed up by personal contact or by detailed postal questionnaire. Where indicated, appropriate investigations including esophagoscopy, barium swallow, and liver, brain, and bone scans were performed.

Multivariate statistical analysis was performed using the GLM procedure (SAS-PC System; SAS Institute Inc, Cary, NC) to look for an effect of any of the multiple variables studied, namely, type of resection, radiation effect score (RES), adventitial and lymph node involvement, tumor size, degree of differentiation, and systemic metastases, on the dependent variable—survival. The Student's χ^2 test was performed on tumor pathology, type of resection, tumor size, RES, and degree of differentiation.

The pathology records of all patients were reviewed, and all sections were reexamined by L.R.M. assisted by J.B.D. Emphasis was placed on diagnosis; degree of differentiation; proximal, distal, and radial clearance; nodal involvement; and radiation effect. The latter was assessed by first scoring on a 0 to 3+ basis the degree of fibrosis, necrosis, partial radiation effect on residual tumor, and surviving tumor. Then a final RES of 0 to 5 was made. Where there was no fibrosis, no necrosis, and viable tumor seen, a 0 value was given to indicate minimal radiation effect. Where there was fibrosis with or without necrosis and no residual viable tumor, a score of 5 was given to indicate an excellent radiation effect. In-between values were obtained by assessing the degree of effect in the changes studied.

Results

There were 68 patients operated on, 56 male and 12 female patients with a mean age of 65.4 years. Three tumors were located in the upper third of the esophagus, 27 in the middle third, and 38 in the lower third, including eight at the gastroesophageal junction. Except for 2 patients in whom fibrotic reaction was noticed, there were no operative difficulties encountered that could be attributed to radiotherapy. There was in-hospital mortality of 14.7% (10/68) with septicemia responsible for 7 of the deaths.

The esophageal malignancies consisted of squamous cell carcinoma (SCC) (43), adenocarcinoma (22: 7 in Bar-

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Table 1. Histology Versus Invasion

	Adventitia		Lymph Nodes	
Histology	Involved	Not Involved	Involved	Not Involved
Squamous cell carcinoma (43)	34 (79%)	9 (21%)	13 (30%)	30 (70%)
Adenocarcinoma				
True esophagus (7)	5	2	2	5
Barrett's (7)	5	2	3	4
Gastroesophageal junction (8)	6	2	6	2
Total adenocarcinoma (22)	16 (73%)	6 (27%)	11 (50%)	11 (50%)
Adenosquamous carcinoma (1)	1	. . .	1	. . .
Malignant fibrous histiocytoma (1)	1	. . .	1	. . .
Pseudosarcoma (1)	. . .	1	. . .	1

rett's esophagus, 7 true adenocarcinomas of the esophagus, 8 adenocarcinomas of gastroesophageal junction), adenosquamous carcinoma (1), malignant fibrohistiocytoma (1), and pseudosarcoma (1). In 90.7% of the cases of SCC and 95.4% of the cases of adenocarcinoma, the tumor had extended beyond the confines of the esophagus, either transgressing the muscle coat or involving regional/distant lymph nodes or both (Table 1). Residual tumor at the line of resection was noticed in 3 of 68 patients and 25% of these resections were considered curative. Squamous cell carcinomas had a better RES than adenocarcinomas (24/43 SCC versus 3/22 adenocarcinoma having an RES > 3; $p < 0.001$). The RES is given in Tables 2 and 3.

In 8 of 68 patients (Table 4), preoperative radiotherapy produced severe fibrosis within the esophagus and the tumor tissue was replaced by irregular masses of keratin often surrounded by macrophages and giant cells (Fig 1). Thus certain palliative resections (because of periesophageal spread or lymph node involvement) were converted into potentially curative resections. Complete follow-up occurred in 62 of 68 patients (91%) with 15 patients alive 7 months to 11 years postoperatively (average follow-up, 32.5 months). We had late death in 37 patients with 29 of them dying of related causes, ie, secondary tumors or recurrence; 3 died of unrelated causes and 5 of unknown causes. Anastomotic leak developed in 8 of 68 patients (11.8%) and late strictures went on to develop in 6 of these. Overall 16 of 62 patients followed up needed esophageal dilations at some stage postoperatively, 14 for benign stricture and 2 for recurrent carcinoma.

On multivariate analysis, factors significantly affecting survival were identified to be the presence of secondary tumors, the type of resection (mean survival of 56 months for curative resection versus 25.8 months for palliative resection; $p < 0.001$), degree of tumor differentiation, and RES (Table 5). Subjecting the RES as an independent variable to the χ^2 test, tumors with RES of 3 to 5 were found to have a much better survival time than tumors with an RES of 0 to 2. In cases of adenocarcinoma, there was only 1 patient who had an RES of 3 and he died 6 months postoperatively of advanced and widespread secondary tumors (Table 6).

Overall 11 patients had local recurrence, and there were 37 secondary tumors in 30 patients. The overall 5-year survival rate was 17.2% and the 10-year survival rate, 4.8%. There was a mean survival of 39.7 months for SCC, 23.9 months for adenocarcinoma, and 32.5 months overall.

Comment

Techniques of radiotherapy are quite varied. Long-term fractionated radiation of 45 Gy in 4 weeks followed by operation after 4 to 8 weeks has been used [2, 3]. This long waiting period may lead to increased chances of lymph

Table 2. Radiation Effect Score

Score	Squamous Cell Carcinoma (43)	Adenocarcinoma (22)	Miscellaneous (3)
0 (Minimal)	0	6	1 (Pseudosarcoma)
1 (Poor)	9	5	1 (Adenosquamous carcinoma)
2 (Mild)	9	8	1 (Malignant fibrous histiocytoma)
3 (Moderate)	15	1	0
4 (Good)	4	2	0
5 (Excellent)	6	0	0

Table 3. Adenocarcinoma—Radiation Effect Score

Score	True Esophageal (7)	Barrett's (7)	Gastroesophageal Junction (8)
0 (Minimal)	1	4	1
1 (Poor)	3	1	1
2 (Mild)	3	0	5
3 (Moderate)	0	0	1
4 (Good)	0	2	0
5 (Excellent)	0	0	0

Table 4. Radiation Fibrosis Group

Patient No.	Size (cm)	Radiation Effect Score	Histological Differentiation	Lymph Node Involvement	Muscle Involvement	Survival (y)
1	3	2	PD	No	Yes	1.2[a]
2	2	4	MD	No	Yes	5.2
3	2.5	3	WD	No	Yes	2.0
4	3	4	MD	No	Yes	3.5[a]
5	3.8	5	WD	No	Yes	2.5
6	1.5	2	PD	Yes	Yes	1.2[a]
7	2	4	WD	No	Yes	14.0
8	3.2	3	MD	No	Yes	8.5[a]

[a] Alive.

MD = moderately differentiated; PD = poorly differentiated; WD = well differentiated.

node and distant metastases [4], and though the incidence of lymph node metastases in the thorax decreased, its incidence in abdominal lymph nodes increased after preoperative radiotherapy [5]. The shorter waiting period of 2 weeks used by us appeared safe as Tsukamoto and Kitagawa (quoted in [4]) have shown that there is no new proliferation of irradiated malignant cells during this time. Higher doses of 50 to 60 Gy add proportionately to the toxicity of radiation [6]. The short-term concentrated radiation therapy used by Kohler, Leb, and Nakayama shortens the period of overall treatment but increases the risk of perforation and hemorrhage (cited in [4]). However, with our protocol of relatively gentle radiotherapy, we had no such radiation-related complications.

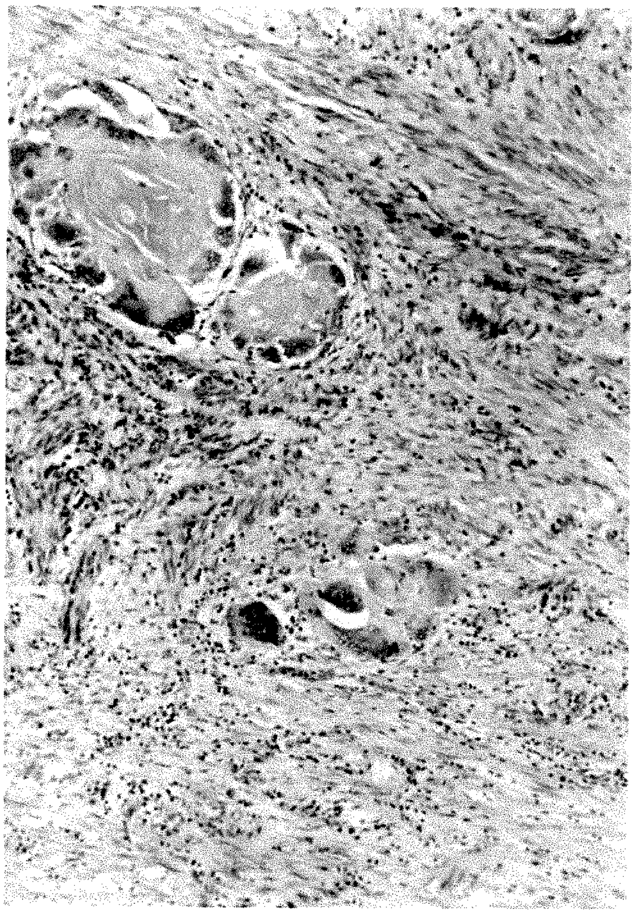

Fig 1. Outer muscularis and adventitia of the esophagus exhibiting excellent radiation effect (radiation effect score = 5): tumor tissue is replaced by fibrosis, inflammatory cells, and masses of keratin surrounded by giant cells. (Hematoxylin and eosin, ×150 before 29% reduction.)

There was an in-hospital mortality of 14.7%. Although extremes of operative mortality (1% to 69%) have been reported. Earlam and Cunha-Melo [7], in their review of 83,783 esophageal cancers reported in 122 studies in the world literature, found an average hospital mortality of 29%. Therefore, in our experience radiotherapy adds neither to intraoperative difficulty nor to hospital mortality; this has been the experience of others also [4, 8].

Incidence of anastomotic leak with hand-sewn anastomosis in our hands was 11.8% and is in accord with the view of Launois and associates [9] that radiotherapy does not contribute to this potentially dangerous complication. Postoperative benign stricture had an incidence of 22.5% for hand-sewn anastomosis, which is rather high and may be attributed to either faulty technique or delayed fibrotic reaction subsequent to radiotherapy. However, this complication was easily managed by dilation and no patient required revision of the anastomosis.

Table 5. Factors Influencing Survival by Multivariate Analysis

Variable	*p* Value
Secondary tumors	0.01
Type of resection	0.03
Tumor differentiation	0.04
Radiation effect score	0.05
Lymph node invasion	0.06
Muscle invasion	0.07
Tumor location	0.07
Tumor size	0.21

Table 6. Survival Versus Radiation Effect Score

Histology	Radiation Effect Score 0 to 2	Radiation Effect Score 3 to 5	Total
Squamous cell carcinoma (mo)	19.9	53.8	39.7
Adenocarcinoma (mo)	26.4	6[a]	23.9

[a] 1 case only.

Akakura and co-workers [4] showed that the incidence of residual tumor at the resected stump was 6.2% in irradiated patients and 24% in nonirradiated patients. They suggested that radiotherapy decreases the incidence of residual tumor at the resected stump. Our figure of 4.4% is in keeping with this view.

We believe in the philosophy that an anatomical obstruction is best relieved surgically. Therefore, 100% of patients thought to be operable on preoperative evaluation underwent resection of their tumor. Though no definite guidelines can be drawn for resectability criteria, in general, all patients were considered suitable for resection of their tumor unless there was evidence of widespread distant metastases or extensive local spread in the form of recurrent laryngeal nerve involvement or total engulfment of vital structures like the aorta. Twenty-five percent of these resections were considered curative as defined by clear proximal and distal lines of resection and no involvement of adventitia or lymph nodes. Higher curative resection rates of 65.1% have been reported [4], but using a much less stringent definition of curative resection. It is our opinion that once the muscle coat is breached or lymph nodes are involved, any resection is essentially palliative. Preoperative radiotherapy, however, increases the incidence of curative resection, and the 25% incidence in our series compares well with the 25.8% incidence reported by Akakura and co-workers [4] using a less stringent definition. The mean survival time for curative resection was more than double that for palliative resection. This has also been the experience of others: Gignoux and associates [6] found a 5-year survival rate of 3% for palliative resections and 21% for curative resections.

The evaluation of radiation effects by histological methods is somewhat subjective, and there does not appear to be any standard scoring system in the literature. Akakura and co-workers [4] quantified the effects of radiotherapy as moderately effective, effective, and very effective but principally based on cellular changes of pyknosis, negative mitoses, and vacuolation, and on changes in the cancer nestle. Sugimachi and colleagues [10] used "ineffective" if viable neoplastic cells were found in less than one third of the lesion and "very effective" if no neoplastic cells could be identified. The RES used in this series of cases had prognostic significance as shown by multivariate analysis ($p = 0.05$). However, when the scores were grouped to give two categories of response, ie, poor response = 0 to 2 and good response = 3 to 5, the χ^2 test showed high prognostic significance ($p < 0.001$). The mean survival of 53.8 months for SCC in the good-response group was nearly three times the survival of 19.3 months for SCC in the poor-response group. Only 1 case of adenocarcinoma was found in the good response group, and the survival time was 6 months. Statistical methods could not be applied to this 1 case to compare with adenocarcinomas in the poor-response group with a mean survival of 20.4 months. Sugimachi and colleagues [10] obtained similar results in their assessment of preoperative radiotherapy. The 5-year survival rate in their "very effective" group was 45.1% as compared with 17.1% and 16.4% in their "moderately effective" and "ineffective" groups.

Contrary to our expectations, on multivariate analysis, lymph node and muscle invasion were identified to affect long-term survival to a statistically less significant level ($p < 0.06$ and 0.07, respectively). In case of lymph node involvement, this may be due to less energetic sampling of lymph nodes on our part and therefore a few involved lymph nodes might have been missed. Muscle invasion, however, may not affect long-term survival as significantly as one has traditionally thought provided lymph nodes are not involved and tumor can be removed in toto. Even Lu and associates [11] failed to identify depth of muscle invasion as a factor affecting long-term survival as long as the tumor was confined to the esophageal wall.

There has been much debate, with little consensus, over the role of radiotherapy in prolonging survival. In one of the very few controlled, randomized, and prospective studies conducted on the subject, no increase in either resectability rate or long-term survival was found [6]. Most studies, however, are uncontrolled, and though occasionally a suggestion of worse survival after radiotherapy is made [12], the majority of others have found beneficial effects of radiotherapy on long-term survival [1, 4], with a 25% 5-year survival in the radiation group versus 13.6% in the nonradiation group [4]. We had a 5-year and 10-year survival of 17.9% and 4.8%, respectively, with a mean survival of 39.7 months for patients with SCC and 23.9 months for those with adenocarcinoma. These figures are very similar to the 17.5% 5-year survival in irradiated patients found by Sugimachi and colleagues [10] and compare favorably with an average 5-year survival of 12%—a figure based on a review of 122 series reported in the world literature [7].

An important feature of our study has been the finding that 8 of 68 patients (11.8%) with advanced tumors showed only fibrosis, necrosis, and nonviable tumor in adventitia or lymph nodes after preoperative radiotherapy. The mean survival time of this group was 57.2 months. Thus certain palliative resections with poor prognosis were converted into potentially curative resections with good long-term survival and an actual survival of 14 years in 1 patient. Total response figures of 13.3% [2] and 14.4% [10]—the latter with a 45.1% 5-year survival rate—support our view that preoperative radiotherapy is a valuable adjunct in the management of esophageal malignancy. Recently, higher total response rates (36% [13]) have been reported in response to combined preoperative chemotherapy and radiotherapy and merit further evaluation.

Local recurrences developed in 11 of 52 patients (21.1%), lymph node metastases in 8 of 52 (15.4%), and distant metastases in 29 of 52 (55.8%). These figures are quite similar to the 23.6% incidence of local recurrences, 42.2% incidence of lymph node metastases, and 35.2% incidence of distant metastases reported by Akakura and associates [4] in their irradiated patients and compare very favorably with the 50% incidence of local recurrence in patients not receiving preoperative radiotherapy [4].

In summary, our method of preoperative radiotherapy used in the management of esophageal malignancy did not seem to add to intraoperative difficulties, in-hospital mortality, or anastomotic leaks. Radiotherapy may have contributed to a high incidence of postoperative benign stricture, but this was easily managed by dilation. Our data suggest that resectability rates are increased, especially the rate of curative resections, and the incidence of residual tumors and local recurrences are reduced. Survival times are improved, marginally overall but quite dramatically in a select group of patients in whom radiotherapy produced total response or converted a potential palliative resection into a curative resection by tumor sterilization. However, this is an uncontrolled study and properly controlled, randomized trials will be needed in the future to clearly address the role of adjuvant therapy in esophageal cancers.

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Emergency Aortocoronary Bypass After Failed Angioplasty

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One thousand two hundred fourteen percutaneous transluminal coronary angioplasties were performed over a 38-month period. Sixty patients required immediate emergency coronary artery bypass grafting after angioplasty failure; 7 of these had evidence of acute myocardial infarction before angioplasty and were excluded from the study. Of the 53 patients remaining, 27 (51%) had electrocardiographic and enzyme evidence of postoperative myocardial infarction. Two patients died (4%), and 10 had postoperative complications (19%). No statistical significance was noted comparing age, sex, incidence of prior myocardial infarction or myocardial dysfunction, time for revascularization, or average number of grafts completed in those with single-vessel (n = 21) versus multiple-vessel (n = 32) coronary artery disease. Postoperatively, those with multiple-vessel disease required intraaortic balloon pump support ($p = 0.06$) and antiarrhythmic medications more frequently than single-vessel patients ($p < 0.01$) and had a higher complication rate ($p < 0.05$). Although not reaching statistical significance, the data also suggest a higher death and postoperative myocardial infarction rate in patients with multiple-vessel disease. Emergency coronary artery bypass grafting after failed percutaneous transluminal coronary angioplasty carries a higher morbidity and mortality than elective coronary artery bypass grafting, particularly for patients with multiple-vessel coronary artery disease.

(Ann Thorac Surg 1991;51:194–9)

Since Gruntzig's [1] clinical application of percutaneous transluminal coronary angioplasty (PTCA) in 1977, widespread use of this technique has taken place, with PTCA being performed in community hospitals as well as major medical centers. Despite advances in instrumentation and proficiency in carrying out these procedures, a considerable number of patients require emergency coronary artery bypass grafting after PTCA failure.

This article reviews our experience with emergency aortocoronary bypass grafting after failed PTCA, with special reference to single-vessel versus multiple-vessel coronary artery disease.

Material and Methods

A retrospective review was performed on 1,214 consecutive patients who underwent PTCA at teaching hospitals affiliated with the University of Louisville. Seventy-two patients had coronary artery bypass grafting procedures performed during the same hospitalization as the PTCA; however, 12 patients were operated on electively and were excluded from this study on that basis. Seven of the remaining 60 patients who required emergency coronary artery bypass grafting had evidence of acute myocardial infarction before attempted PTCA, and these were excluded from this study as well. The remaining 53 patients made up the study group; all were in stable condition with no electrocardiographic or enzyme evidence of acute myocardial infarction before attempted PTCA.

Failure of PTCA and the decision to proceed with immediate coronary artery bypass grafting rested on the judgment of the cardiologist, in consultation with the cardiac surgeon. The patients were taken immediately to the operating room, and no attempts at preoperative placement of intraaortic balloon pumps were made. "Time for revascularization" indicates that interval of time commencing when the cardiologist recognized failure and called for the surgeon and ending when the patient came off cardiopulmonary bypass. Operative strategy included bypassing the acutely ischemic coronary vessel first, followed by perfusion of the graft through a Y-connector off of the aortic inflow catheter to perfuse the jeopardized myocardium.

Patients were considered in unstable condition en route to the operating room if they had cardiac arrest with cardiopulmonary resuscitation in progress, recalcitrant ventricular fibrillation or ventricular tachycardia, or hypotension of less than 80 mm Hg on pressor agents. All grafts consisted of saphenous vein aortocoronary bypass grafts, and no patients had a previous bypass operation.

The patients were grouped into categories of single-vessel or multiple-vessel disease based on the presence or absence of 70% or greater stenosis in two or more major vessels. Tandem lesions in the same vessel were considered "single-vessel" involvement. Electrocardiograms and ventriculograms were analyzed for the presence of old myocardial infarction or clinically significant myocardial dysfunction before PTCA. Patients were classified as

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Table 1. Preoperative Clinical Characteristics

Characteristic	Multiple Vessel (n = 32)	Single Vessel (n = 21)	p Value	All Patients (n = 53)
Age (y ± SD)	60.1 ± 10.2	57.1 ± 11.3	NS	58.9 ± 10.7
Age range (y)	40–78	40–78	NS	40–78
Sex (% male)	75%	76%	NS	75
Old MI (%)	28%	19%	NS	25
Myocardial dysfunction before PTCA (%)[a]	22%	19%	NS	25

[a] Ejection fraction < 0.40.

MI = myocardial infarction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

having clinically significant myocardial dysfunction if their resting ejection fraction was 0.40 or less.

All charts were then reviewed to determine the incidence of postoperative death and complications. The diagnosis of acute myocardial infarction was made by the presence of new, persistent Q waves with loss of R-wave force, as well as elevation of the level of total creatine kinase with greater than 5% MB fraction or "flipped" lactate dehydrogenase$_1$/lactate dehydrogenase$_2$ isoenzyme pattern. The use of intraaortic balloon pump support, inotropic agents, and antiarrhythmic medication was determined by examination of intensive care unit records.

Statistical analysis was performed using the nonpaired Student's t test to assess quantitative differences between the single-vessel and multiple-vessel groups, and the χ^2 test to assess differences in categorical variables with data considered significant when p was less than or equal to 0.05.

Results

Of the 53 patients, 21 had single-vessel disease and 32 had multiple-vessel disease. A comparison of the characteristics of each group is shown in Table 1. No significant difference in age, sex, or prior myocardial infarction or myocardial dysfunction was noted between the groups.

The conditions that prompted termination of PTCA and proceeding with subsequent coronary artery bypass grafting are listed in Table 2. There was a trend showing a higher incidence of preoperative cardiac arrest in the multiple-vessel group (16% versus 5%). All 6 of the patients who had cardiac arrest in the catheterization laboratory had angioplasty of a left anterior descending coronary artery lesion, and 4 of these 6 had evidence of old myocardial infarction on electrocardiograms taken before attempted PTCA. Thirty-eight percent of the patients were in unstable condition in the catheterization laboratory and en route to the operating room (Table 3).

No significant difference was noted in the average time required for revascularization of the single-vessel and multiple-vessel groups.

Table 2. Indications for Termination of Percutaneous Transluminal Coronary Angioplasty and Proceeding With Coronary Artery Bypass Grafting

Indication	Multiple Vessel (n = 32)	Single Vessel (n = 21)
Acute occlusion	19	16
Intimal dissection	17	9
Unstable angina	9	9
Arrhythmias (recurrent VT/VF)	4	4
Broken guidewire	0	1
RV puncture—tamponade	1	0
Perforated LAD—tamponade	1	0
Cardiac arrest—CPR to operating room	5	1

CPR = cardiopulmonary resuscitation; LAD = left anterior descending coronary artery; RV = right ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

Postoperatively, there were two deaths in the multiple-vessel patient group and none in the single-vessel group, for an overall mortality of 3.8%. Both deaths in the multiple-vessel patient group occurred in patients who had old myocardial infarctions prior to the failed PTCA attempt.

The first patient, 62 years old, had 2-vessel disease of the left anterior descending and right coronary arteries and had angioplasty of both of these lesions, leading to cardiac arrest in the catheterization laboratory. Despite complete revascularization and the use of inotropic agents and intraaortic balloon pumping, he could not be weaned from bypass and died on the operating table.

The second patient, 45 years old, had 3-vessel disease and underwent angioplasty of a proximal left anterior descending coronary artery lesion, leading to cardiac arrest in the catheterization laboratory. Despite complete revascularization he could not be separated from bypass and a left ventricular assist device was placed. The patient died in 24 hours with biventricular failure.

Morbidity, as reflected by postoperative myocardial in-

Table 3. Outstanding Characteristics of Operations

Characteristic	Multiple Vessel (n = 32)	Single Vessel (n = 21)	p Value	All Patients (n = 53)
Unstable to operating room[a]	41%	33%	NS	38%
Average time for revascularization (min ± SD)	178 ± 70	192 ± 74	NS	184 ± 71
Average No. of grafts per patient (± SD)	2.1 ± 0.7	1.9 ± 0.9	NS	2.0 ± 0.8

[a] Blood pressure <80 mm Hg on pressors, cardiac arrest, or recurrent ventricular tachycardia or ventricular fibrillation.

NS = not significant; SD = standard deviation.

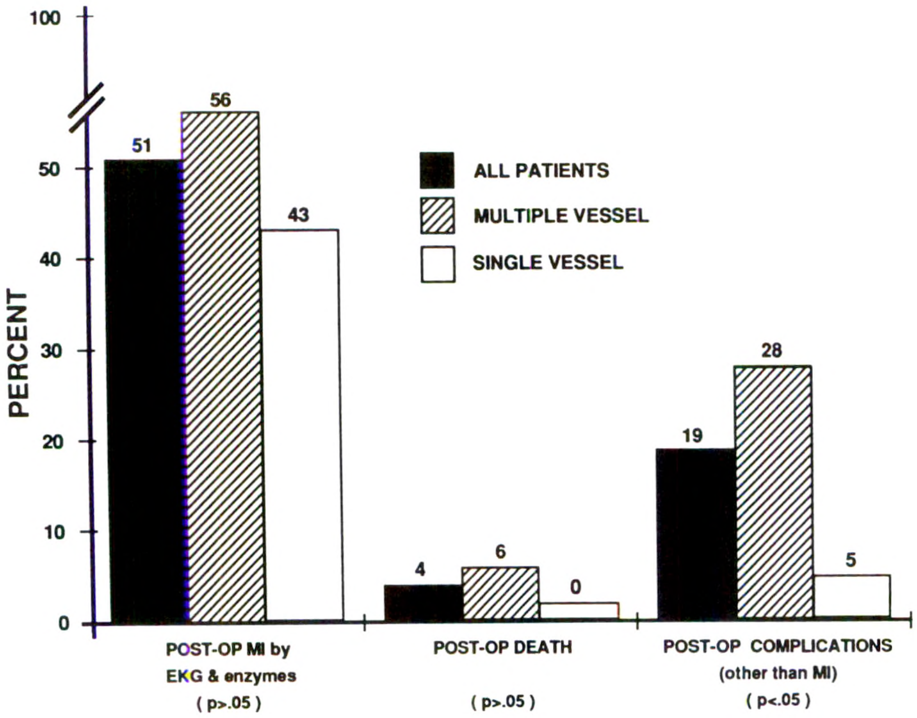

Fig 1. Postoperative myocardial infarction (MI), death, and complication rates with respect to extent of coronary artery disease. (EKG = *electrocardiogram.)*

farction and complication rates, was high for both single- and multiple-vessel groups (Fig 1). Overall, 51% of the patients sustained a perioperative myocardial infarction by electrocardiographic and enzyme criteria. Compared with single-vessel patients, the multiple-vessel disease patients had a slightly higher incidence of postoperative myocardial infarction.

The incidence of other complications was significantly higher in the multiple-vessel group. One leg wound infection developed in the single-vessel group. In the multiple-vessel group, complications included postoperative bundle-branch blocks in 4 patients, strokes in 3 patients, reoperation for mediastinal bleeding in 1 patient, one groin wound infection with sepsis, one groin hematoma, paralyzed diaphragm in 1 patient, central line sepsis in 1 patient, and 1 case of foot drop after intraaortic balloon pump support.

Eight of 32 patients (25%) in the multiple-vessel group required intraaortic balloon pump support postoperatively, compared with 1/21 (5%) in the single-vessel group ($p = 0.06$). A majority of patients required inotropic support in the postoperative period (75% of multiple-vessel patients versus 57% of single-vessel patients). Twenty-three percent of multiple-vessel patients required antiarrhythmic medications greater than 48 hours postoperatively, compared with none in the single-vessel group ($p < 0.01$).

Comparing patient variables, no factors were identified that could accurately predict which patients would likely suffer a myocardial infarction after emergency coronary artery bypass grafting for failed angioplasty; however, those who were in unstable condition en route to the operating room tended to have a higher myocardial infarction rate (Table 4).

Comment

Incidence of Angioplasty Failure

A collective review indicates that the overall failure rate leading to emergency coronary artery bypass grafting is 5% (Table 5). Coronary artery bypass grafting is defined as emergent, by most clinical series, if the patient requires operation within 24 hours after PTCA. In the present study, we also attempted to define what percentage of failures were "in extremis," as preparations were made for emergency operation. Thirty-eight percent of patients in our study were in unstable condition before emergency coronary artery bypass grafting. This is consistent with the incidence of hemodynamic instability reported by Connor [13] (23%), Pelletier [7] (26%), Bredlau [4] (33%), Murphy [15] (41%), and their associates.

Intimal dissection and acute occlusion were most often cited as reasons for proceeding with coronary artery bypass grafting in our study. These primary indications were also most frequent in the studies of Parsonnet [12], Pelletier [7], Lazar [11], Golding [9], Jones [2], Cowley [3], and their associates. Many patients had multiple indications for termination of PTCA and proceeding with coronary artery bypass grafting (ie, dissection plus arrhythmia, occlusion plus unstable angina).

In the present review, 1 patient had a perforated left anterior descending artery, 1 had a punctured right ventricle, and 1 had a broken guidewire that lodged in the left main coronary artery.

Table 4. Univariate Analysis of Risk Factors Associated With Acute Myocardial Infarction After Failed PTCA and Emergency CABG

Variable	Postoperative Myocardial Infarction (27 Patients)	No Postoperative Myocardial Infarction (26 Patients)	Significance
Mean age (y ± SD)	59.3 ± 11.4	58.5 ± 10.0	NS
Men/women	19/8	21/5	NS
Previous myocardial infarction	5	8	NS
Previous myocardial dysfunction	5	8	NS
Unstable to operating room	13	7	NS
Mean number of stenotic vessels	1.8 ± 0.7	1.7 ± 0.8	NS
Presence of LAD stenosis	20	20	NS
Presence of CX stenosis	9	10	NS
Presence of RCA stenosis	18	13	NS
Dilation of LAD	18	18	NS
Dilation of CX	5	6	NS
Dilation of RCA	10	9	NS
Multivessel PTCA	7	7	NS
Time for revascularization (min ± SD)	185.6 ± 75	183 ± 66	NS

CABG = coronary artery bypass grafting; CX = circumflex coronary artery; LAD = left anterior descending coronary artery; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; SD = standard deviation.

Emergency Revascularization

In the present review, the average time from recognition of PTCA failure to completion of the last bypass graft was 184 minutes. Others have defined "ischemic time" differently, making comparison of revascularization times difficult; however, the times reported by Lazar and Haan [11], Golding and associates [9], Murphy and co-workers [15], and Pelletier and colleagues [7] (average, 142 to 180 minutes) are similar to that in the present review. When patients are subjected to emergency coronary artery bypass grafting after failed angioplasty, the goal of complete revascularization is not attained in all cases. In the present study, the average number of grafts performed was 2.1 for multiple-vessel patients. Similarly, Page [10], Parsonnet [12], Pelletier [7], Lazar [11], and their associates all reported an average of 2.0 grafts or less per patient despite a significantly higher expected number of grafts based on extent of stenotic disease. Zorn and others have shown that incomplete revascularization in multiple-vessel disease patients adversely affects 5-year survival [16]. Since this study, our current operative strategy is to perform complete revascularization of all clinically significant coronary lesions.

Postoperative Death

In the present study, the death rate after coronary artery bypass grafting for failed angioplasty was 2/53 (3.8%). As shown in Table 5, there were 63 deaths in the collective group of 987 patients who underwent emergency coronary artery bypass grafting for failed PTCA (6.4%).

Postoperative Complication Rates

The reported incidence of postoperative myocardial infarction after emergency coronary artery bypass grafting for failed PTCA ranges from 18% to 63%, with an average

Table 5. Summary of Previously Published Studies[a]

First Author	Year	PTCAs Performed	Emergency CABG	Postoperative MI	Postoperative Death
Jones [2]	1984	777	41 (5.3%)	9/41 (18%)	1/41 (2.4%)
Cowley [3]	1984	3,079	202 (6.6%)	90/202 (45%)	13/202 (6.4%)
Bredlau [4]	1985	3,500	96 (2.7%)	47/96 (49%)	2/96 (2.1%)
Acinapura [5]	1985	198	21 (10.6%)	8/21 (38%)	0 (0%)
Shiu [6]	1985	240	14 (5.8%)	5/14 (36%)	1/14 (7.1%)
Pelletier [7]	1985	299	35 (11.7%)	10/35 (29%)	0 (0%)
Killen [8]	1985	NA	115	46/115 (40%)	13/115 (11.3%)
Golding [9]	1986	1,831	81 (4.4%)	35/81 (57%)	2/81 (2.5%)
Page [10]	1986	NA	44	14/44 (32%)	3/44 (6.8%)
Lazar [11]	1987	1,045	24 (2.3%)	15/24 (63%)	3/24 (12.5%)
Parsonnet [12]	1988	958	67 (7.0%)	19/67 (28%)	8/67 (11.9%)
Connor [13]	1988	996	146 (14.7%)	57/146 (39%)	4/146 (4.4%)
Naunheim [14]	1989	2,418	103 (4.3%)	23/103 (22%)	11/103 (10.7%)
Greene (present study)	1989	1,214	53 (4.4%)	27/53 (51%)	2/53 (3.8%)
Average			5%	40%	6.4%

[a] Other studies, which include patients reported above, have been omitted to prevent duplication.

CABG = coronary artery bypass grafting; MI = myocardial infarction; NA = not available in text of paper; PTCA = percutaneous transluminal coronary angioplasty.

of 40% (see Table 5). In the present study, 43% of single-vessel patients had electrocardiographic and enzyme evidence of acute postoperative myocardial infarction, compared with 56% of multiple-vessel patients. Other authors have noted a higher postoperative myocardial infarction rate in patients with multiple-vessel disease as well [9]. One possible explanation of this apparent higher postoperative myocardial infarction rate in multiple-vessel patients is the lack of adequate collateral circulation. If total occlusion results from PTCA of a vessel, concomitant partial stenoses in other vessels may not allow sufficient blood flow to supply the myocardium made ischemic by the occluded vessel. This is particularly true when hypotension further reduces perfusion through the stenosed collateral vessels.

Data by Alcan and associates [1] and Murphy and colleagues [15] indicate that intraaortic balloon pump support during preparation for emergency coronary artery bypass grafting after failed PTCA reduces the incidence of postoperative myocardial infarction. Although sample sizes were small, Murphy and colleagues showed a 50% to 20% reduction of Q-wave infarction with balloon pumping. Complications of intraaortic balloon pump insertion were noted in 6% of Murphy and colleagues' patients and 21% in Alcan and associates' report, although complication rates of up to 36% using intraaortic balloon pumping have been reported by others [18, 19].

Other techniques to improve oxygenation or decrease myocardial oxygen demands during preparation for operation include intracoronary nitroglycerin, institution of femoral bypass, placement of guidewire stents or "bail out" catheters across the occlusion, and direct infusion of oxygenated blood or fluorocarbons into the coronary arteries [20–22].

Ferguson and others [23] reported on the use of intravascular stents across stenoses after failed PTCA. They noted that the stent allowed stabilization of the patients and performance of a more optimal bypass procedure, including use of the internal mammary artery.

Numerous authors have attempted to define those pre-angioplasty variables that may increase the likelihood of perioperative myocardial infarction if emergency coronary artery bypass grafting becomes necessary. Page and associates [10] reported that all 3 patients who died in their series had angioplasty of the left anterior descending coronary artery, and both deaths in the present series occurred after PTCA of the left anterior descending coronary artery as well. In the present study, dilation of specific vessels did not correlate with the incidence of perioperative myocardial infarction, nor did the dilation of more than one lesion lead to an increase in perioperative myocardial infarction (see Table 4). Major complications, other than myocardial infarction, occurred in 11% to 50% of patients requiring emergency coronary artery bypass grafting after PTCA failure in the studies by Golding [9], Pelletier [7], Parsonnet [12], Brahos [24], and their associates. In the present study, 19% of all patients had major nonmyocardial infarction complications. When this is analyzed with respect to extent of disease, multiple-vessel patients had a significantly higher incidence of complications compared with single-vessel patients (28% versus 5%, $p < 0.05$). Bredlau and associates [4] performed multivariate analysis of 3,500 patients who underwent PTCA and noted that the strongest pre-PTCA predictors of complications were multiple-vessel coronary artery disease, lesion eccentricity, and lesion calcification.

In the present study, 17% of all patients required intraaortic balloon pump support postoperatively (5% of single-vessel versus 25% of multiple-vessel patients, $p = 0.06$). This is slightly higher than the percentages reported by Jones [2] (4%), Parsonnet [12] (7.5%), Brahos [24] (10.3%), and their associates. The requirements for postoperative inotropic support reported by Parsonnet and associates (55%) and Brahos and co-workers (24%) are also somewhat lower than that in our review (68%). Once again, multiple-vessel patients had a higher incidence of requiring vasopressors (75% versus 57% for single-vessel patients).

In the present study, 50% of all patients required antiarrhythmics postoperatively; however, after 48 hours, only patients in the multiple-vessel group continued to require suppression of ventricular arrhythmias (23% versus 0% of single-vessel patients, $p < 0.05$). Three patients in the multiple-vessel group required antiarrhythmics at the time of discharge.

The average length of stay was significantly longer for patients in the multiple-vessel group compared with the single-vessel group (15.0 ± 9.9 days versus 10.5 ± 2.9 days, $p < 0.05$). This average length of stay after coronary artery bypass grafting for failed angioplasty is similar to that reported by Parsonnet and associates [12] (15.3 ± 1.1 days).

In summary, emergency coronary artery bypass grafting after failed PTCA carries a greater risk of perioperative death and complications than elective coronary artery bypass grafting. Our study indicates 4.4% of patients undergoing PTCA require emergency coronary artery bypass grafting; 4% of those will die, and 51% will sustain perioperative myocardial infarction. Patients will multiple-vessel disease have higher death and complication rates after emergency coronary artery bypass grafting for failed PTCA than do those with single-vessel disease.

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Long-Term Results of Ionescu-Shiley Valve in the Tricuspid Position

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A retrospective analysis of the long-term results of using the Ionescu-Shiley pericardial bioprosthesis in the tricuspid position was carried out on 73 patients (8 men, 65 women). Of these procedures, ten were tricuspid valve replacement alone and the remainder were in combination with other valve procedures. The mean follow-up was 9.6 years (range, 4 to 18 years). The mean age of the patients was 53 years (range, 27 to 78 years). Seventy-one of the patients suffered tricuspid valve dysfunction from rheumatic heart disease. There were 13 postoperative deaths (within 30 days), giving a mortality rate of 17.8%. The actuarial survival at 10 years was 71% ± 4.2%. Of the survivors, 49 (79.6%) were in functional class I or II. Primary tissue valve failure in the tricuspid position occurred in 1 patient 12 years after implantation and required reoperation. In another patient bioprosthetic tricuspid valve endocarditis developed. There was no incidence of thromboembolic complications. We conclude that the Ionescu-Shiley pericardial bioprosthesis was a satisfactory prosthesis in the tricuspid position in patients with acquired valvar dysfunction.

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In recent years, tricuspid valve replacement has been performed less frequently not only because of the earlier surgical intervention of mitral and aortic valve diseases [1], as prolonged mitral valve dysfunction tends to lead to tricuspid incompetence [2], but also because of rapid advances in valve conservation techniques [3–6]. In our unit, tricuspid valve repair is performed whenever a satisfactory result can be achieved [7]. In the presence of gross valvar destruction [8], as for instance in *Staphylococcus aureus* endocarditis [9], tricuspid valve replacement may still be required. Although long-term results may be satisfactory in some centers [10], the use of mechanical prostheses in the tricuspid position can be associated with a high incidence of thrombotic complications [1, 11, 12]. Bioprosthetic valves [8] including homografts [13] are regarded as more satisfactory in the tricuspid position. With these considerations, we review our experience of tricuspid valve replacement using the Ionescu-Shiley pericardial bioprosthesis over a 15-year period.

Patients and Methods

Between 1971 and 1985, 73 patients underwent tricuspid valve replacement with the Ionescu-Shiley pericardial bioprosthesis. There were 65 female and 8 male patients, with a mean age of 53 years (range, 27 to 78 years).

Table 1 shows the types of procedures performed in these patients. In 28 patients, these were the first operations performed, whereas the other patients were undergoing repeat operations, including patients who underwent previous closed mitral valvotomy. The Ionescu-Shiley pericardial bioprostheses were used in all cases. Of the patients who underwent tricuspid valve replacement alone, 7 had previous mitral valve replacements. Four patients also had a concomitant coronary artery operation. Except in 2 patients, the tricuspid valve damage was from rheumatic heart disease. One of the remaining patients suffered tricuspid incompetence after stab injury, and the other had endocarditis due to the insertion of an endocardial pacing system.

Preoperatively, 12 patients (16.4%) were in New York Heart Association (NYHA) class IV, 59 (80.8%) in class III, and 2 (2.8%) in class II associated with gross tricuspid incompetence and right ventricular overload. Sixty-five patients were in atrial fibrillation. The diagnosis of gross tricuspid dysfunction was made preoperatively by a combination of echocardiography and cardiac catheterization and confirmed by digital examination and visualization of the valves during operation. All patients had abnormal valve leaflets, including fibrosis, commissural fusion, and cusp retraction. Seven patients had a previous tricuspid valve operation, including 4 with De Vega annuloplasty and 3 with previous mechanical valves. At operation, pressures before bypass were as follows (in mm Hg ± standard error): right atrial: 8.5 ± 0.66 (range, 1 to 22); right ventricular: 35/2.7 ± 1.5/0.73 (range, 20 to 65/0 to 20); and left atrial: 18 ± 1 (range, 6 to 38).

The technique of tricuspid valve replacement has been described in detail previously [14]. After completion of the aortic or mitral valve replacements as appropriate, the aortic cross-clamp was removed and the heart allowed to beat. The right atrium was opened and the valve assessed. After the valve was excised the bioprosthesis was

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Table 1. Types of Valve Replacements

Valve Replacement	No. of Patients	Repeat Operations
TVR	10	7
MVR + TVR	45	30
MVR + AVR + TVR	17	8
AVR + TVR	1	0
Total	73	45

AVR = aortic valve replacement; MVR = mitral valve replacement; TVR = tricuspid valve replacement.

sutured into place using a continuous suture except for a small segment along the conduction bundle, where interrupted sutures were used. While these sutures were tied, if rhythm changes were observed on the electrocardiogram, the offending suture was removed and a more superficial suture inserted, thus avoiding injury to the conduction system.

Forty-eight patients had tricuspid valve replacements with 29-mm bioprostheses, 20 with 27-mm bioprostheses, and 5 with 31-mm bioprostheses.

Patients who survived were assessed clinically at yearly follow-up. Only those with symptoms or signs of valve dysfunction were investigated further with echocardiography and cardiac catheterization. Patients were anticoagulated with warfarin sodium for 3 months after operation.

Results

A total of thirteen patients died within 30 days of operation, giving an early mortality rate of 17.8%. The causes of these early deaths were low output failure (8 patients), myocardial infarction (2), intractable ventricular tachycardia (1), septicemia (1), and perforated duodenal ulcer (1). Deaths occurred in 8 patients after mitral and tricuspid valve replacements, of which four were repeat operations, and in 3 after triple-valve replacements, of which two were repeat operations, one after repeat tricuspid valve replacement and one after primary aortic and tricuspid valve replacement. Of these patients 61.5% were in NYHA class IV and 38.5% were in class III preoperatively. Neurological deficits developed in a further 3 patients, 2 of whom fully recovered; the third had residual hemiparesis. Persistent atrioventricular conduction defects occurred in 6 patients, all of whom had preoperative evidence of conduction abnormalities. These patients required the placement of permanent pacemakers.

Follow-up was complete except for 1 patient who lived abroad, with a mean of 9.6 years (range, 4 to 18 years). Five patients died within the follow-up period, 2 due to valvar dysfunction from calcific degeneration (1 mitral and aortic valve dysfunction and the other after reoperation for mitral valve dysfunction). Three patients died 2 years after operation, 1 after 3 years, and the last after 10 years. All five tricuspid valves inspected at postmortem examination failed to show any serious degeneration 2 to 10 years after implantation. Of the survivors, mitral bioprosthetic valve dysfunction occurred in 7 patients, 6 of whom underwent reoperation. Echocardiographic studies preoperatively and digital assessement intraoperatively revealed satisfactory bioprosthetic tricuspid valve structure and function. We do not routinely replace a bioprosthetic valve that has been implanted for longer that 10 years unless it is found to be malfunctioning. Endocarditis of the tricuspid valve developed in 1 patient 4 years after replacement for stab injury of the valve. Primary tricuspid bioprosthetic failure requiring reoperation occurred in 1 patient 12 years after operation. Calcific degeneration and cusp fusion were observed. No patient suffered thromboembolic complications.

Figure 1 shows the actuarial survival curve of this series of patients. At 10 years, the actuarial survival rate was 71% ± 4.2% (standard error). Clinical assessment of the survivors shows 20 patients to be in NYHA class I, 27 in class II, 6 in class III, and 2 in class IV awaiting reoperation for mitral valve dysfunction. There was no echocardiographic evidence of bioprosthetic tricuspid valve abnormalities in these patients in classes III and IV.

Comment

The long-term follow-up and assessment of patients after tricuspid valve operations is difficult because the inevitable associated mitral or aortic valve disease tends to dominate the clinical picture. With rare exceptions, acquired tricuspid valve disease is always associated with severe mitral valve disease and, in the majority of pa-

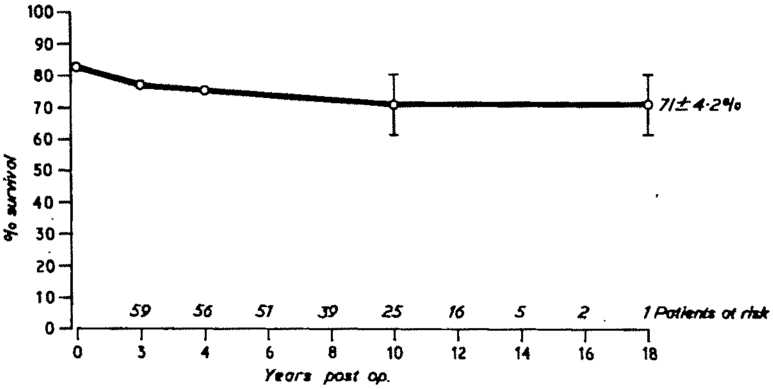

Fig 1. Actuarial survival curve of patients after tricuspid valve replacements with or without other valve procedures. At 10 years, the acturial survival was 71.4% ± 4.2%.

tients; with aortic disease as well [15]. Early observation that tricuspid regurgitation improved after mitral valve operations for advanced mitral valve dysfunction led to the conservative approach in tricuspid valve dysfunction [16]. The poor outcome of this approach led others to advocate the all-in-one approach to multivalvar lesions in reducing operative mortality [17]. Furthermore, the difficulty of assessing the degree of tricuspid valve dysfunction, depending in some series on digital palpation at operation [15], means that interpretation of outcome may not be very satisfactory. Recent advances in echocardiographic techniques allow better assessment and quantification of such dysfunction in mechanical [12] and bioprosthetic valves [18]. As in many published series [1, 5, 6], we found a preponderence of female patients in our series.

The mortality figures in most published series reflect those associated with multivalvar procedures and poor condition of the patients. Recent advances in surgical techniques and myocardial protection mean that tricuspid valve operations do not necessarily increase the operative risk in patients already requiring repair or replacement of both the aortic and mitral valve [13]. This was our experience. The operative risk for patients requiring mitral and tricupid operations certainly appears greater than the risk for mitral operations alone [6]. Our operative mortality of 17.8% is comparable with published figures [1, 5, 8]. This is associated with poor preoperative functional status, with 61.5% of the deaths in patients who were in class IV and 38.5% in class III. This has previously been observed [13]. In this series, age, concomitant coronary artery operation, and the number of previous procedures did not appear to affect the outcome of the operation.

The use of mechanical prostheses in the tricuspid position in multivalvar procedures is associated not only with a high early mortality of 23.7% [19] to 34% [20] but also with high incidences of thrombotic complications [1, 12] and valve dysfunction from tissue ingrowth [10] and incorporation of the cage in the wall of the right ventricle [17]. The use of bioprosthetic valves in the tricuspid position, even when mechanical valves are used concomitantly in the mitral and aortic position, appears to result in lower operative mortality [21, 22]. Long-term survival appears to be satisfactory [8] and comparable with that of patients who underwent tricuspid annuloplasty [23]. Our observation of 71% actuarial survival at 10 years is comparable with that achieved with De Vega annuloplasty [7] and compares favorably with other series [10, 11]. This may be a reflection of the earlier surgical intervention in this series of patients, with a high proportion of patients in NYHA class III (80.8%). Recent series, however, show superior results with annuloplasty for functional tricuspid regurgitation [5]. The good clinical outcome achieved in patients in this series, with 79.6% of the survivors in NYHA class I and class II, is comparable with previous reports [1, 19]. The lack of thromboembolic complications without prolonged anticoagulation has been most encouraging, even though the majority of the patients (50 of 55) were in atrial fibrillation. This observation is based on clinical assessment, however, with its consequent limitations.

With improvement in the techniques of annuloplasty with or without the use of rings [3–6], conservation of the tricuspid valve should be attempted whenever possible. When such an approach is unsuitable, we believe that the Ionescu-Shiley pericardial bioprosthesis or other bioprosthetic valves of similar characteristics are good substitutes in the tricuspid position.

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Circulatory Support 1991

The Second International Conference on Circulatory Support Devices in End-Stage Heart Disease

San Francisco Marriott Hotel, San Francisco, California
November 15–17, 1991 (weekend meeting)

Circulatory Support 1991 will be a comprehensive multidisciplinary meeting focusing on the clinical applications of the entire spectrum of circulatory support devices. Surgeons, cardiologists, anesthesiologists, intensivists, perfusionists, engineers, and operating room and intensive care nurses are encouraged to attend as individuals or as a team.

The meeting is sponsored by The Society of Thoracic Surgeons under the direction of its Committee on Circulatory Assist Devices and Artificial Hearts. Committee members are: D. Glenn Pennington, MD, Chairman; Jack G. Copeland, MD; Charles Hahn, MD; J. Donald Hill, MD; George J. Magovern, MD; Peer M. Portner, PhD; and Glenn Rahmoeller.

For this weekend meeting, the Saturday morning segment entitled "Problem Cases" will include panel and audience discussions of four major subject areas: patient selection; anticoagulation management, bleeding, and thromboembolic risk; infections—prophylaxes and treatment; and management of secondary organ dysfunction. An outstanding international panel has been chosen to represent a broad spectrum of opinions for each subject.

Late Saturday morning and early afternoon, video sessions on the working details and proposed indications for support devices that are currently in use or development will be presented. A report of the current circulatory support device registry will be given. Breakout sessions of smaller groups will follow and focus on how to use external nonpulsatile circulatory support, external pulsatile circulatory support, and internal pulsatile circulatory support.

The Sunday sessions from 7:45 AM to 1:00 PM will be devoted to state-of-the-art presentations covering: emergency resuscitation techniques, heparinless bypass, the Hemopump experience, postoperative use of the Biopump, the VAD experience in Japan, optimizing hemodynamics and assessing myocardial recovery, right heart management during LVAD support, circulatory support in children, bridge to transplantation with the Thoratec VAD and with the Symbion TAH, chronic support with the TCI left ventricular assist system, the Novacor left ventricular assist system, and the Penn State TAH.

Poster presentations concerning a wide variety of subjects related to circulatory support as well as commercial exhibits demonstrating currently available devices will be available during breaks. Full CME credit will be provided for attendees.

For registration details concerning poster submissions and other available meeting information contact: The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; telephone: (312) 644-6610.

Endothelial Cell Viability in the Rat Aortic Wall

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Aortic allografts may offer advantages over prosthetic materials for aortic valve replacement or reconstruction with a valved aortic conduit. Cellular viability may partly determine long-term allograft performance. To evaluate endothelial cell viability in a rat model, valved aortic conduits were subjected to collagenase digestion. The resulting endothelial cell suspension was labeled with *Griffonia simplicifolia* agglutinin-fluorescein isothiocyanate (GSA-FITC), a marker specific for vascular endothelial cells of the rat. The cells were then incubated with propidium iodide, which is excluded by viable cells. Flow cytometry evaluated endothelial cell viability by determination of percentage of GSA-FITC–positive cells that were negative for propidium iodide. Aortas were studied immediately after harvest or after storage at 4°C in a nutrient medium for 3 to 21 days. Percentage of viable endothelial cells showed a progressive decline with increasing duration of storage. These results demonstrate flow cytometric measurement of endothelial cell viability, a factor of possible importance in assessing allograft storage methods, and show that endothelial viability declines with prolonged storage at 4°C in a nutrient medium.

(Ann Thorac Surg 1991;51:204–7)

Aortic allografts have been used extensively for aortic valve replacement, conduit reconstruction of the aortic root, and relief of right ventricular outflow obstruction. The longevity of these tissues appears to be limited, although the precise factors that determine these limits are unknown.

One factor that some investigators consider to be important in determining allograft durability is the degree of cellular viability [1, 2]. Aortic allografts comprise a heterogeneous population of cells, and determination of graft "viability" logically requires understanding viability of those specific populations [3].

This study was performed to quantify the viability of endothelial cells of valved aortic segments in a rat model using flow cytometric techniques. This method was applied to evaluate endothelial cell viability in aortas preserved by a storage technique similar to that employed clinically in some centers.

Material and Methods

Adult male Lewis rats received general anesthesia with intraperitoneal injection of 3.6% chloral hydrate (1 mL/100 g body weight). The heart and thoracic aorta were exposed through a median sternotomy. The entire thoracic aorta including the aortic valve and extending to the diaphragm was excised and placed in cold heparinized saline solution. The tissue was then placed in 4°C RPMI 1640 culture medium with 10% fetal calf serum and the following antibiotics: gentamicin (160 mg/L), piperacillin (1,000 mg/L), oxacillin (50 mg/L), metronidazole (200 mg/L), and amphotericin B (100 mg/L). Preliminary studies on tissue treated with these antibiotics found no bacterial growth after as much as 3 weeks of storage at 4°C. After 24 hours, the tissue was transferred to RPMI 1640 culture medium with 10% fetal calf serum at 4°C. The tissue was maintained in this solution for 3, 5, 7, 10, 14, or 21 days. An additional group of specimens was studied immediately after harvest. Nine to 11 specimens were studied at each time interval.

At the designated time, the aorta was placed in 0.1% type I collagenase (Sigma Corporation, St. Louis, MO) at 38°C for 7 minutes. The endothelial layer was then removed from the aorta by gentle rubbing with a glass rod and transferred to a centrifuge tube with 10 mL of phosphate buffer solution. The endothelial cell suspension was centrifuged at 1,500 rpm for 5 minutes. The supernatant was discarded and the sample resuspended in 100 μL of iced *Griffonia simplicifolia* agglutinin-fluorescein isothiocyanate (GSA-FITC, Sigma Corporation), 20 μg/mL, for 30 minutes. The cells were washed with phosphate buffer and centrifuged twice to remove any GSA-FITC not bound to the endothelial cell membranes. The cells were resuspended in 0.5 mL of propidium iodide (Sigma Corporation), 50 μg/mL, and analyzed within 3 to 5 minutes by flow cytometry.

The suspension was placed in a pressurized cell suspension chamber and passed through a 67-μm millipore filter into the flow chamber. The cells were passed through an argon ion laser (488 nm wavelength at 400 mW power). The emitted light passed through a 525-nm band-pass filter for GSA-FITC analysis and through a 635-nm band-pass filter for propidium iodide analysis. Signal intensities were recorded by a MADAD II acquisition system. The data were then stored in list mode, gated, and integrated by a Coulter Fluorescence Activated Cell Sorter (Coulter Cytometry, Hialeah, FL).

Cells that were positive for GSA-FITC and negative for

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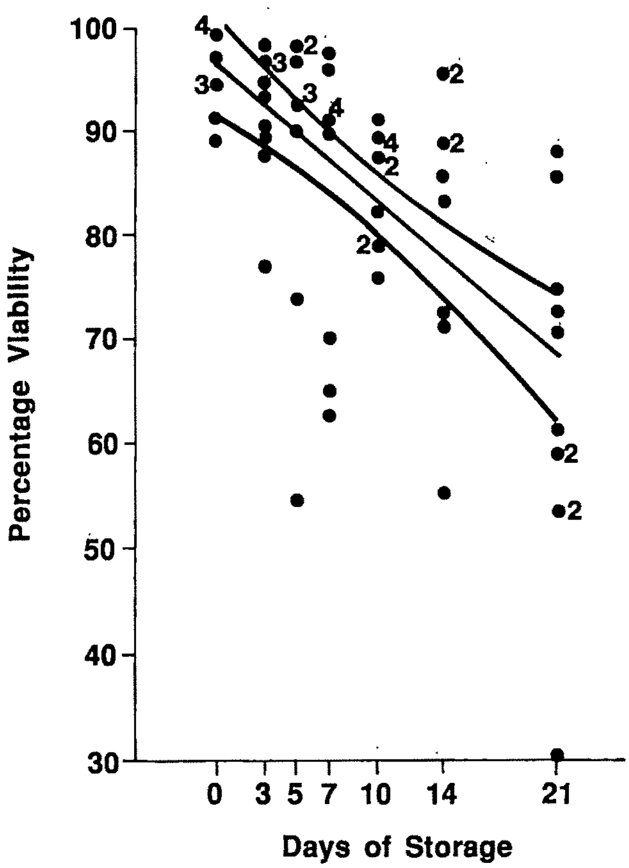

Fig 1. Relation of percentage endothelial cell viability to duration of storage. Surrounding 90% confidence limits are shown. Percentage viability = −1.345 × days of storage + 96.281 (r = −0.63; p < 0.001).

propidium iodide were considered to be viable endothelial cells, whereas those positive for both GSA-FITC and propidium iodide were considered nonviable endothelial cells. A minimum of 1,000 endothelial cells was analyzed for each specimen, and the percent endothelial viability was recorded. The mean and standard error for each duration of storage were calculated. The percent viability was correlated with duration of storage using least square linear regression analysis. The Pearson correlation coefficient and p value were calculated. A p value less than 0.05 was considered statistically significant.

Animals received humane care in compliance with the "Guide for the care and use of laboratory animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

The percentages of endothelial cells determined to be viable were control (n = 11): 95 ± 1; 3 days (n = 10): 92 ± 2; 5 days (n = 9): 88 ± 5; 7 days (n = 11): 86 ± 4; 10 days (n = 11): 86 ± 2; 14 days (n = 10): 83 ± 4; and 21 days (n = 11): 64 ± 5. There was a significant negative correlation between duration of storage and endothelial cell viability (Fig 1; $r = -0.63$; $p < 0.001$).

Comment

Cellular viability of aortic allografts has generally been considered an important determinant of long-term graft function [1, 2]. "Viability," however, is unlikely to be an all-or-none quality. Furthermore, distinctions may need to be drawn between viability of fibroblasts and that of endothelial cells, the two major cell populations composing the aortic valve [3].

Endothelial cells and fibroblasts may not necessarily be preserved to the same degree by a given method of graft preservation. Mochtar and associates [4], using a preservation method similar to that employed in the present study, found that fibroblast viability declined markedly after more than 2 weeks of storage. Because the present investigation found a similar decline in endothelial cell viability over the same period, it is possible that endothelial cells and fibroblasts have a corresponding response to storage techniques. Further studies may distinguish factors that can cause a convergent or divergent outcome for these two cell populations. It has been suggested that fibroblasts may be more important than endothelial cells in determining allograft longevity [2]. Fibroblasts are not easily studied using flow cytometric methods because of the difficulty in obtaining a single-cell suspension.

Viable endothelial cells may be important to long-term graft performance by providing nutrition to the fibroblast, inhibiting calcification, and preventing thrombosis [5, 6]. Some of the factors that may affect endothelial cell viability include duration of tissue ischemia before preservation [7], method of sterilization [8], and method of storage [7, 9].

The earliest methods of allograft sterilization, such as ethylene oxide or β-propiolactone, caused tissue damage [10] and probably shortened graft longevity [11]. Some more recent antibiotic sterilization regimens also proved to be cytotoxic [12]. The antibiotic combination employed in this study avoids some of the more harmful effects of many earlier methods. However, it remains possible that even these drugs may cause some cellular damage. Measurement of endothelial viability may be helpful in defining the optimal antibiotic protocol, because sterilization is apparently indispensable if transmission of potentially dangerous bacteria is to be avoided [13].

Enhanced endothelial viability may, however, contribute to increased antigenicity of allografts. The endothelium is an important site of antigen presentation and is perhaps the most immunogenic component of vascular structures [14]. Previous work from this laboratory observed the effects of prolonged storage of rat aortic valve allografts on second-set skin graft rejection. This study used the same methods of valve harvesting and storage used in the present investigation, followed by heterotopic transplantation into the abdominal aortas of recipient animals. With increased duration of storage, the duration of skin graft survival progressively increased, indicating a lesser degree of immunological stimulation [15]. The present investigation may thus be used to explain in a quantitative way the relationship between endothelial viability and allograft immunogenicity.

There are problems, however, in attempting to draw simple conclusions regarding these studies. First, the heterotopic implantation of aortic valve tissue requires implantation of a small amount of ventricular muscle as well. This muscle is itself a strong immunogenic stimulus [16]. Second, fetal calf serum as used in the storage medium has been implicated as an antigen [17] that may be associated with a somewhat higher likelihood of primary tissue failure [18]. Fetal calf serum may, however, be important in preserving both fibroblast [19, 20] and endothelial viability. Fetal calf serum was therefore used in the present study, as it has been used in clinical applications [20, 21]. Finally, immunogenicity may be determined to a greater degree by fibroblasts than by endothelium. The great disparity in mass of fibroblasts compared with that of endothelial cells may make the former the predominant immunogenic influence.

The study of Innes and co-workers [8] was one of the first to describe the changes in endothelial cell structure during the harvest, sterilization, and storage of allograft valves. These investigators, using the then-available methods of freezing the valves for later use, found a significant degree of endothelial loss from the valve leaflets. Yankah and colleagues employed Alcian blue dye exclusion on a monolayer preparation to quantitate viability of rat [7] and human [9] aortic endothelial cells. They demonstrated a progressive decline in cellular viability during storage in a nutrient medium at 4°C. They also demonstrated a decline in viability with longer periods of warm storage time before refrigeration.

Flow cytometry is useful in the examination of endothelial cells because it provides precise quantitative analysis not available by other techniques. Because *Griffonia simplicifolia* has a high affinity for the α-D-galactopyranosyl residues of rat endothelial cells, it was selected as a marker for these cells [22]. GSA-FITC is a functionally monomeric lectin, and using it avoids problems of agglutination that may occur with multimeric lectins [23]. Propidium iodide, a dye with high affinity for double-stranded nucleic acids, is excluded by cells with intact membrane function, and therefore those that are viable [24]. It is likely that this and related techniques can be applied to further studies of allografts involving both animal models and humans.

Certain limitations to this study must be acknowledged. The aortic wall, rather than the aortic valve leaflets, was undoubtedly the major source of endothelial cells studied in this preparation. The viability of aortic wall endothelium may not be the same as that of the valve leaflets. In addition, collagenase dispersion of endothelial cells may not affect viable and nonviable endothelial cells equally. Therefore the population of endothelial cells subjected to flow cytometric analysis may be unrepresentative of in situ endothelial cells. Finally, some nonviable cells are capable of excluding dyes like propidium iodide [25], which may indicate that the numerical assessment provided by this methodology represents an upper limit of the true degree of cellular viability. However, the combination of the fluorescent markers used in this study has been found to allow accurate determination of cell viability [26].

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Notice From the American Board of Thoracic Surgery Regarding Trainees and Candidates for Certification Who Are Called to Military Service Related to the Persian Gulf Crisis

The Board appreciates the concern of those who have received emergency call to military service. They may be assured that the Board will exercise the same sympathetic consideration as was given to candidates, in recognition of their special contribution to their country, during the Korean and Viet Nam conflicts with regard to deadlines, applications, examinations, and interruption training.

Harvey W. Bender, Jr, MD
Chairman
The American Board of Thoracic Surgery

Technique for Use of the Inferior Epigastric Artery as a Coronary Bypass Graft

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A search for a coronary bypass conduit with increased longevity has resulted in harvest of the inferior epigastric artery. The artery is dissected through a paramedian incision with retraction of the rectus muscle to the lateral side. As the inferior epigastric artery courses superiorly, it may lie in one of three positions in relation to the rectus muscle. Distal coronary anastomoses using this conduit are conventional, and the proximal anastomosis may be made to the aorta or end-to-side to an internal mammary artery or venous conduit. After preparation with dilute papaverine-Plasmalyte solution proximal sizes have ranged from 2.5 to 3.25 mm (internal diameter), and distal inferior epigastric artery sizes measured 1.5 to 2.5 mm (internal diameter). The lengths of the conduit ranged from 11.5 to 17.0 cm. Eighteen patients aged 41 to 74 years had inferior epigastric artery grafts to 19 coronary arteries. The indications for use were absent or poor-quality vein, young age with an attempt to limit vein graft, and avoidance of use of bilateral internal mammary artery grafts in insulin-dependent diabetic patients. There was one sterile wound hematoma and one late wound infection. There were no other infections and no deaths. Three patients studied postoperatively revealed widely patent inferior epigastric artery grafts.

(Ann Thorac Surg 1991;51;208–14)

Although the saphenous vein is the most common conduit used as a coronary bypass graft, the late patency is poorer than that of arterial grafts. Thus the search continues for suitable arterial conduits as multiple revascularizations are necessary and prosthetic materials have not proven satisfactory. The inferior epigastric artery (IEA) was first reported for use as a coronary arterial bypass graft in 1988 [1]. The idea for such use as a conduit for coronary bypass was also noted during the course of kidney transplantation and successfully used by Vincent and associates [2]. The purpose of this report is to graphically demonstrate the technique that we have used for harvest and use of the IEA as a coronary bypass graft.

Anatomy

The branches of the external iliac artery arise at its distal end near the inguinal (Poupart's) ligament. The branches are: (1) the inferior (deep) epigastric artery, (2) the deep circumflex iliac artery, and (3) small variable branches to neighboring muscle and lymph nodes. The IEA arises from the medial side of the external iliac artery and immediately passes on the medial side of the ductus deferens in the male or the round ligament in the female. It ascends between the transversalis fascia and peritoneum and courses medially accompanied by its satellite veins. The two inferior epigastric veins that lie on either side of the epigastric artery end in a single trunk and veer slightly medially before entering the external iliac vein. The IEA pierces the transversalis fascia and passes in front of the linea semicircularis (Douglas' fold). Thereafter, it courses upward between the rectus muscle and the posterior rectus sheath. It eventually enters the rectus muscle to anastomose with the superior epigastric artery from the internal mammary artery (IMA). Branches of the IEA include (1) the external spermatic artery, which runs with the spermatic duct, and (2) the pubic branch, which passes below or above the femoral ring to the back of the pubis.

The IEA courses superiorly. It may lie in one of three positions. First, it may pierce the substance of the rectus muscle at the level of the umbilicus and continue within that muscle near the anterior surface until it anastomoses with the superior epigastric artery. Second, it may continue well above the level of the umbilicus on the posterior side of the rectus as it gives off twigs to that muscle. Third, it may bifurcate 3 to 5 cm below the umbilicus with one branch coursing near or along the posterior rectus sheath and the other branch continuing within the substance of the rectus muscle. This last anatomical condition is of interest to the surgeon as both branches may be harvested for use as a natural Y graft.

Harvest of the Inferior Epigastric Artery

A left paramedian incision is made slightly to the left of the midline of the rectus muscle for harvest of the left IEA. Harvest of the right IEA is identical to that of the left. The incision is angled slightly as a "hockey stick" toward the point at which the femoral artery arises from under the inguinal ligament. However, the lower end of the incision is stopped about 5 cm above the level of the inguinal ligament (Fig 1). The rectus sheath is opened throughout the length of the incision, and the rectus muscle is dissected only from its medial bed and gently retracted

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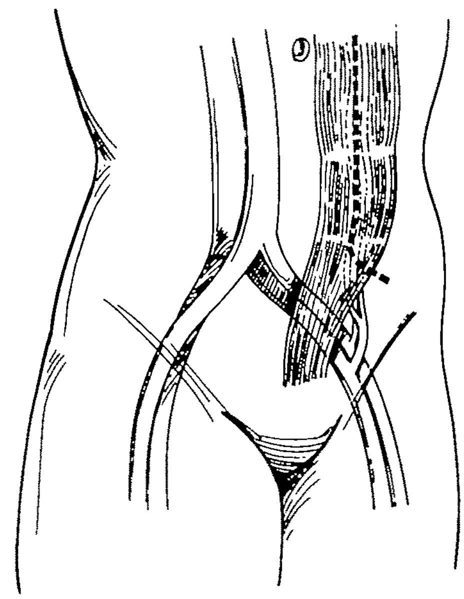


Fig 1. Incision for harvest of the left inferior epigastric artery is made slightly lateral to the midline of the rectus muscle and is angled toward the femoral vessels. The incision stops well above the femoral crease.

laterally. Care is taken not to use undue traction on the rectus muscle at this point for small penetrating branches from the IEA into the rectus muscle may be avulsed and damage the graft. Posterior peritoneal branches lying on the preperitoneal membranes are used to lead one to the parent artery as soon as possible. These branches are ligated adjacent to the IEA with 4-0 silk and divided. Electrocautery is used to free the interdigitations of the rectus from the rectus sheath (Fig 2).

The IEA is harvested as a pedicle with the two accompanying veins, first toward its origin from the external iliac artery. Traction on the rectus sheath with clamps and traction toward the midline on the preperitoneal membranes aid in exposure. Lateral branches are divided and ligated, and the inferior-most branch to the rectus muscle is ligated and divided. The pedicle is then seen diving posteriorly and laterally toward the inguinal canal (Fig 3). At this point exposure may become difficult. The lower 4 to 5 cm of the rectus muscle may be separated laterally to aid exposure of the origin of the IEA (Fig 4A). The external spermatic artery and the pubic branch are identified and ligated. If convenient, they are divided 5 to 10 mm from their origins. The IEA is ligated separately and divided. Finally, the IEA is dissected to its origin from the external iliac artery and suture ligated with a 2-0 silk ligature. The artery is divided, exposure is changed back to the midline by retracting the rectus laterally, and a 2-mm soft plastic needle (catalog no. 31002; DLP, Inc, Grand Rapids, MI) is introduced into the inferior epigastric artery and tied in place. Heparinized Plasmalyte solution (Baxter Healthcare Corp, Edwards Division, Irvine, CA) is injected (Fig 4B).

When the patient has had a concomitant saphenous vein removed from the upper part of the leg, the upper saphenous incision may be angled toward the inguinal ligament, and the proximal femoral artery and distal external iliac artery may be identified and exposed. The proximal end of the IEA may be ligated and divided using that approach. Removal of a small wedge of external iliac artery has been advocated to offer a "cuff" for a proximal aortic anastomosis. Thereafter the external iliac artery is closed using interrupted Prolene sutures [2]. A pericardial patch has also been used to repair such an external iliac arterial defect [3]. We have avoided this technique because it has three potential hazards. First, it is not feasible to heparinize the patient at this point of the operation, and there is some liability associated with temporary clamping of the iliac and femoral vessel. Second, the distal iliac artery often has atherosclerosis, and a more intricate arterial repair may become necessary. Distal atherosclero-

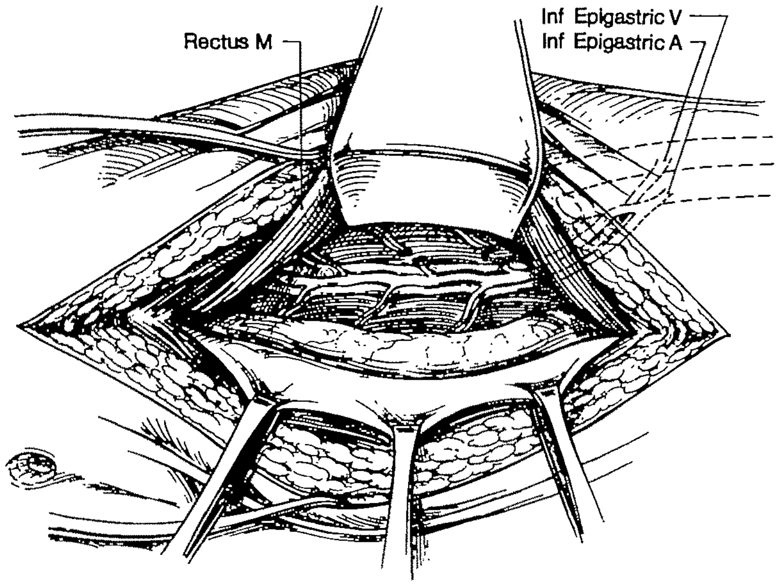


Fig 2. Harvest of the inferior epigastric artery is begun by retracting the rectus laterally after its fascia is opened directly anterior for the length of the incision. Undue traction on the rectus muscle (M) at this point can avulse penetrating branches. (A = artery; Inf = inferior; V = vein.)

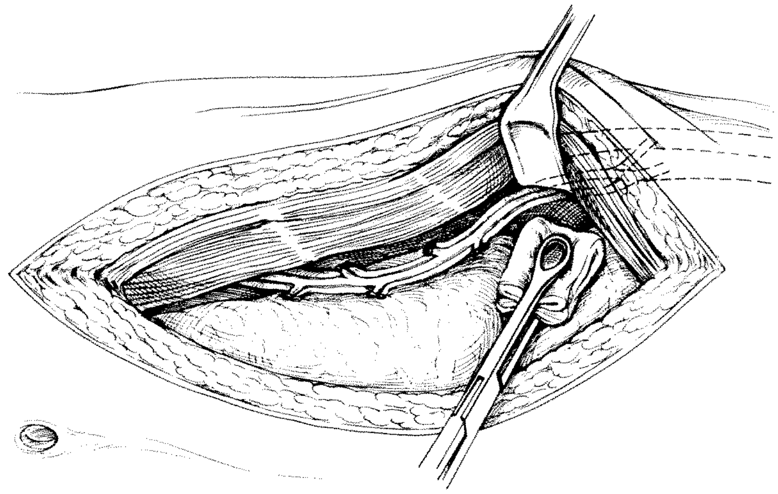


Fig 3. Dissection is first carried inferiorly as the inferior epigastric artery branches are ligated and divided. Traction with a sponge-stick on the peritoneal tissues enhances exposure.

sis in the iliac artery cuff would make a less than optimal bypass graft.

Harvest of the distal IEA is continued by ligating its penetrating rectus branches and dividing them between silk sutures (Fig 5). If the IEA continues on the posterior rectus fascia the final part of the dissection is relatively easy. However, usually this vessel enters the rectus muscle, and the harvest has to be done by elevating the rectus, tilting the table to the left, and continuing to search and divide the branches as the artery courses up to the level of the umbilicus. Occasionally, the artery at this point meanders laterally, and exposure can be facilitated by dissecting the lateral border of the rectus muscle for 4 to 5 cm and retracting the rectus muscle medially (Fig 6). If the IEA is near the surface of the rectus muscle, the rectus fibers are separated from an anterior approach, and the artery is dissected as it makes its way in the substance of that muscle (Fig 7). On occasion when the IEA sends equal size branches superiorly, both branches may be dissected for use as a natural Y graft.

Finally, the dissection is completed by dividing the artery and ligating its upper branches and parent trunk. It is then placed on a towel, a 1:40 dilution of body temperature papaverine-Plasmalyte solution is injected, and the graft is dilated. Any bleeding areas are ligated. Care is taken at this point to ensure against any twist, and the graft is marked with a single small silk suture taken throughout its length or with a methylene blue sterile marking pen. Closure of the wound is carried out with interrupted rectus fascial sutures. A Jackson-Pratt drain is left in place through the belly of the rectus muscle to end near the origin of the IEA. Routinely, the wound is closed before cardiopulmonary bypass is begun (Fig 8).

Anastomoses

The distal anastomoses are sutured using a 5- to 6-mm coronary arteriotomy with 8-0 polypropylene suture on a BV-2–size needle. The anastomosis is begun at the graft heel and sewn circumferentially around the toe with both ends terminating in the midportion of the coronary arteriotomy. The final sutures are tied down, and patency in

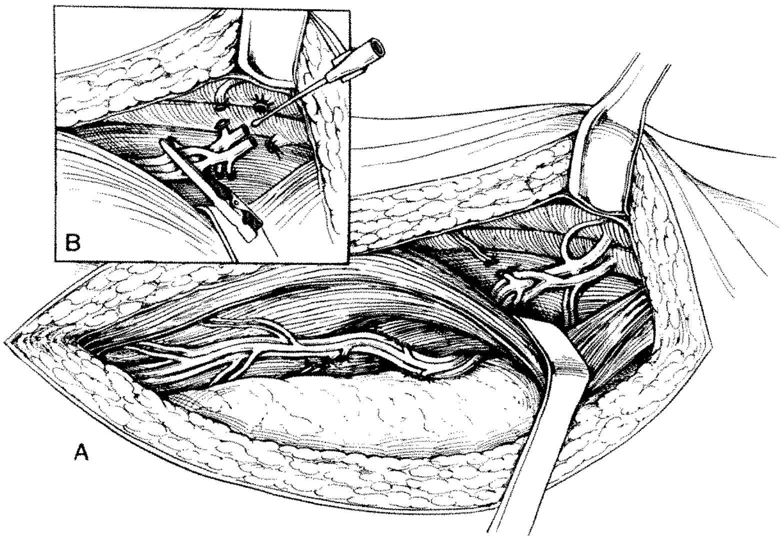


Fig 4. (A) To facilitate dissection, the lateral border of the left rectus muscle is dissected away from its fascia for 4 to 5 cm. The origin of the inferior epigastric artery is exposed through this approach. (B) The external spermatic artery and the pubic branch of the inferior epigastric artery are ligated as well as the inferior epigastric vein. The inferior epigastric artery itself is ligated at its origin, and after a 2-mm soft, plastic olive-tip needle is tied in place, the graft is withdrawn from under the rectus muscle.

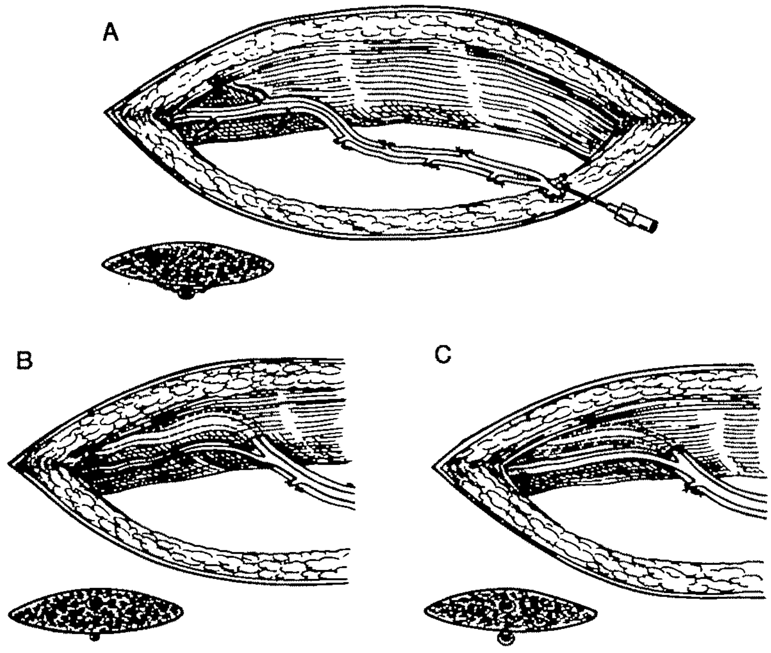


Fig 5. The inferior epigastric artery may take three different routes: (A) It may remain as a sizable artery ascending under the rectus muscle on the posterior rectus sheath. (B) The larger branch may pierce the rectus muscle and travel within the rectus muscle belly (this is the more common anatomical finding). (C) The inferior epigastric artery may divide into equal branches as both course superiorly.

all three directions is checked with the appropriate size probe. Injection of Plasmalyte solution is used to search for leaks. Two to three 5-0 polypropylene sutures are used to tack the grafts to the epicardium to ensure an appropriate lie using the silk marking suture or the methylene blue mark as a guideline (Fig 9).

Proximal anastomoses are performed by two methods. A proximal anastomosis is made to the ascending aorta when the aorta is of normal thickness and without disease. The anastomosis is made after punching a segment of aorta with a 4-mm punch. The proximal IEA is split open down into the external spermatic arterial branch or pubic branch (whichever is the largest). This gives a patulous opening for the proximal anastomosis. The graft is then anastomosed to the ascending aorta using 6-0 polypropylene suture on the BV-1 needle. If subsequent saphenous anastomoses are performed, the patency of the IEA anastomosis is checked with the appropriate size probe through the area punched on the aorta for the saphenous graft before that anastomosis is performed (Fig 10).

Proximal anastomoses of the IEA are made end-to-side to an internal mammary artery graft (or saphenous vein graft) when (1) the ascending aorta is diseased or (2) the IEA is not of sufficient length to reach the aorta without tension. A 1-cm arteriotomy is made on the posterior surface of the IMA (or saphenous vein graft) between small bulldog clamps. The proximal IEA to IMA graft

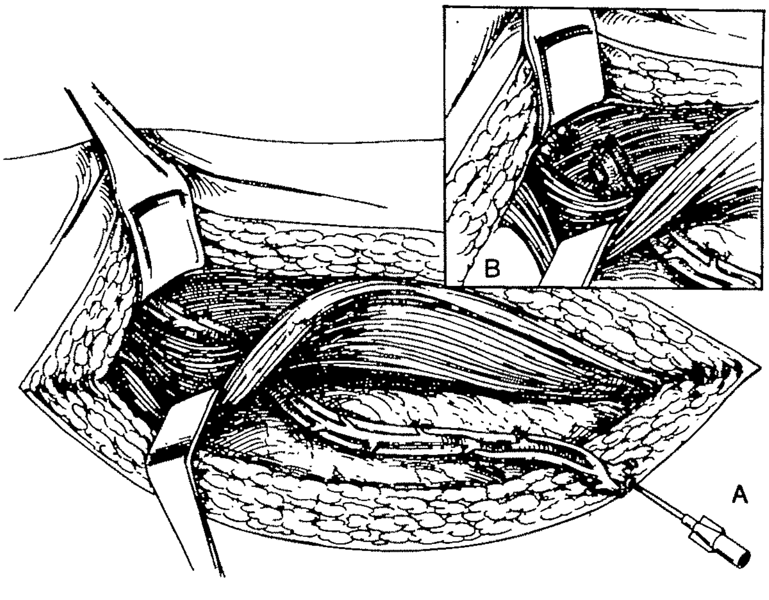
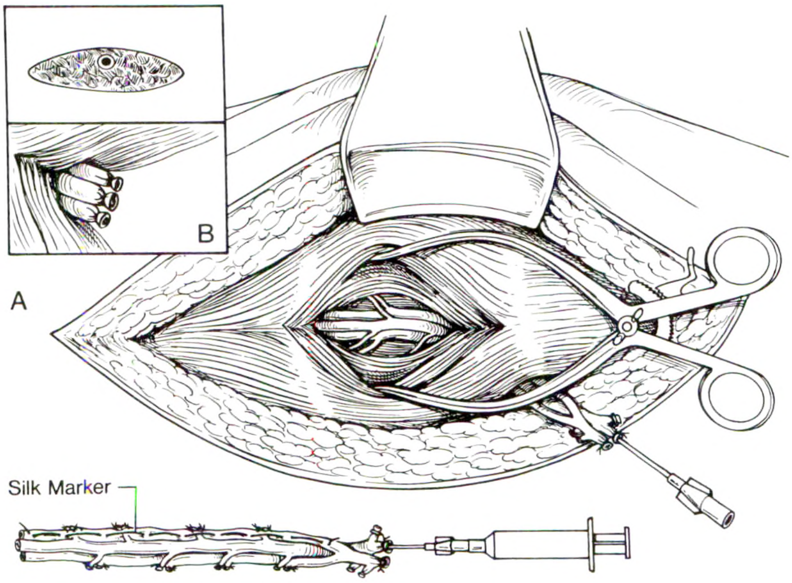


Fig 6. (A) In some instances it is necessary to enhance exposure superiorly by separating the rectus muscle from its lateral attachment for a 4 to 5 cm distance. It is then retracted medially. (B) The upper end of the inferior epigastric artery is divided and ligated to complete harvest of the graft.

Fig 7. (A) At times the rectus muscle may be separated on its anterior surface and the dissection carried out superiorly to harvest a shallow intrarectus inferior epigastric artery. The dissection may become tedious because of numerous branches. (B) After the graft is ligated and divided distally, it is marked with silk suture or sterile marking pen on one surface to protect against an inadvertent twist.



anastomosis is then performed using continuous 7-0 Prolene. The anastomosis is begun at the heel and continued around the toe to end in the midportion of the IMA arteriotomy.

Before the final sutures are tied down, patency is assured in all three directions with the appropriate size probe. A small tacking suture is placed from the IEA to the parent graft to ensure against any tension on the anastomosis (Fig 11).

An alternative technique is that of performing the inferior epigastric–IMA proximal anastomoses before cardiopulmonary bypass is begun. The IMA is laid out over a moist lap after arterial cannulation. Free flow of the IMA is checked and ensured to be greater than 150 mL/min. Lie and length of the proposed artificial Y arterial graft system must now be carefully checked to avoid error. An arteri-

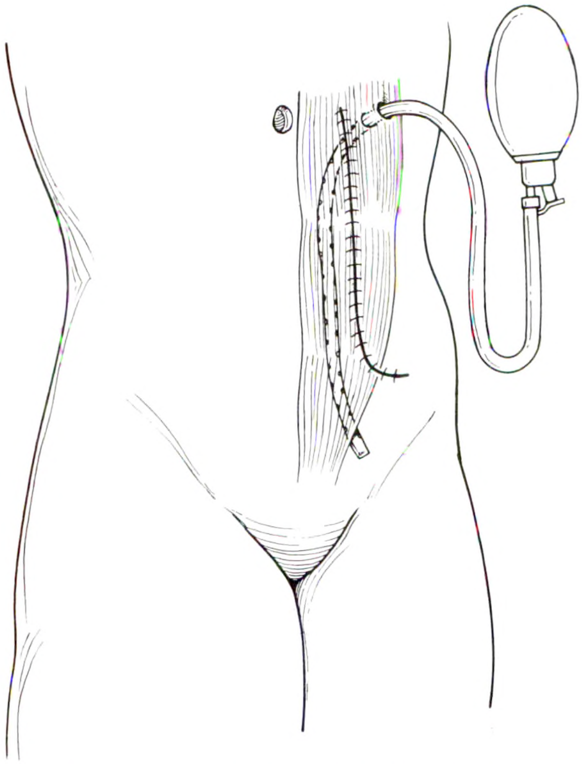


Fig 8. A Jackson-Pratt closed drainage system is used to prevent hematoma formation in the postoperative period. The drain is placed through the rectus muscle to end 2 cm from the distal external iliac vessels.

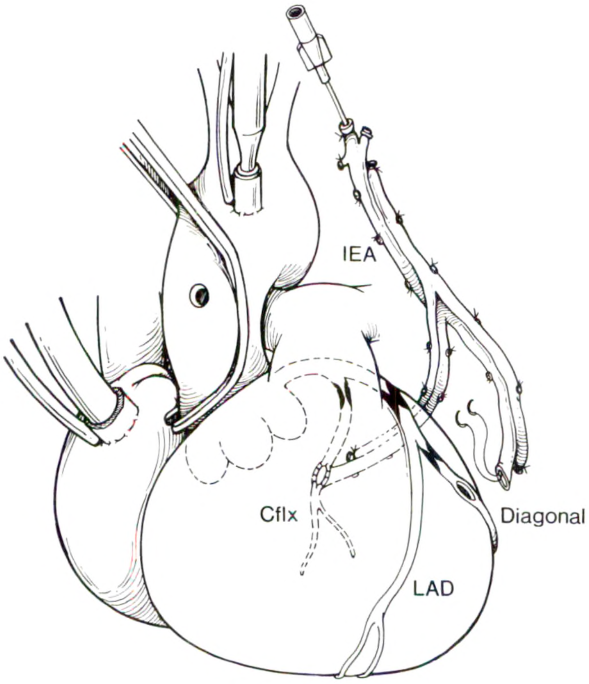


Fig 9. A natural Y inferior epigastric artery (IEA) may be anastomosed to two coronary arteries to increase the number of arterial conduits used for revascularization. (Cflx = circumflex coronary artery; LAD = left anterior descending coronary artery.)

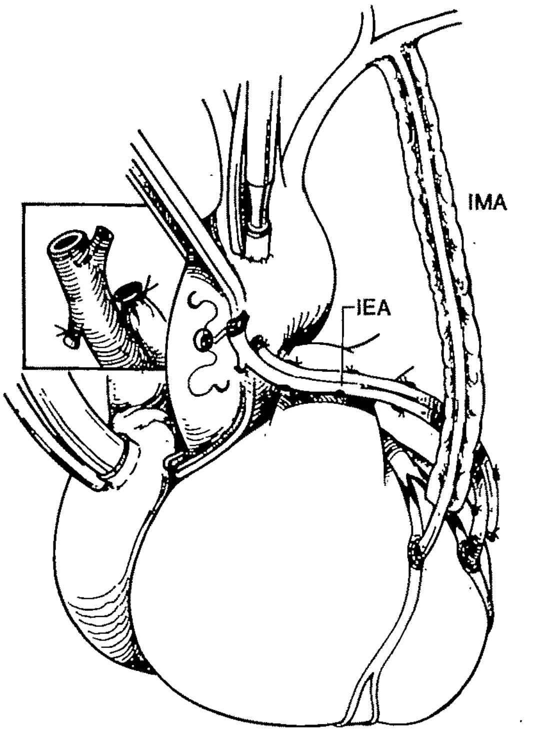


Fig 10. The inferior epigastric artery (IEA) has been opened across a side branch to make the "mouth" larger for the proximal anastomosis. That anastomosis is performed using 6-0 polypropylene suture on a BV-1 needle. (IMA = internal mammary artery.)

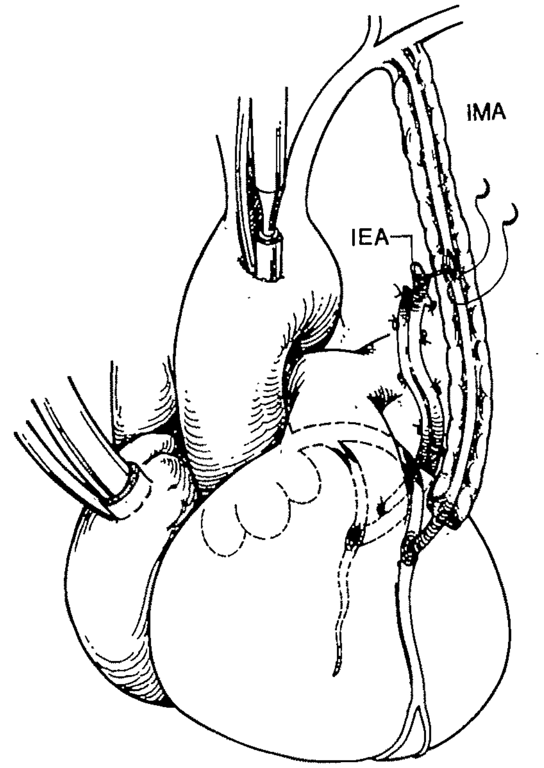


Fig 11. The inferior epigastric artery (IEA) is anastomosed distally to a circumflex branch, and in this patient it is not long enough to reach the ascending aorta without tension on the graft. The proximal anastomosis is therefore made to the posterior surface of the internal mammary artery (IMA) graft, which is supplying the left anterior descending coronary artery.

otomy is performed on the IMA posterior surface, and with 7-0 Prolene the proximal IEA is anastomosed to the IMA using the same basic technique. The anastomosis is checked for bleeding before cardiopulmonary bypass is begun. After cardiopulmonary bypass is instituted and cardioplegia has been given, the distal inferior epigastric anastomosis is made to a ramus marginalis, diagonal branch of the left anterior descending, or marginal branch of the circumflex coronary artery. The IMA limb of the artificial Y is then anastomosed to the left anterior descending coronary artery.

An alternative technique has been reported for fashioning an aortic–IEA anastomosis. The aortic–IEA proximal anastomosis has been constructed after a patch of saphenous vein or bovine pericardium is sutured to the IEA graft itself before cardiopulmonary bypass is begun. This new cuff of other material is then anastomosed to the aorta [4].

Clinical Experience

Eighteen patients aged 41 to 74 years have had IEA grafts to 19 coronary arteries. Three patients were female. Coronary arteries bypassed were: circumflex marginal branches, 10; diagonal branches, 4; ramus marginalis, 2; right coronary, 2; and posterior descending, 1. One natural Y IEA graft was performed to the ramus marginalis and to the first marginal branch of the circumflex coronary artery. Proximal arterial sizes have ranged from 2.50 to 3.5 mm (internal diameter) and distal IEA sizes measured 1.5 to 2.5 mm (internal diameter) (Fig 12). Lengths of grafts ranged from 11.5 to 17 cm. Indications for use of the IEA have been: (1) absent or poor quality vein, (2) young age with an attempt to limit the use of vein grafts, and (3) avoidance of use of bilateral IMA grafts in the obese insulin-dependent diabetic patient. Three patients had

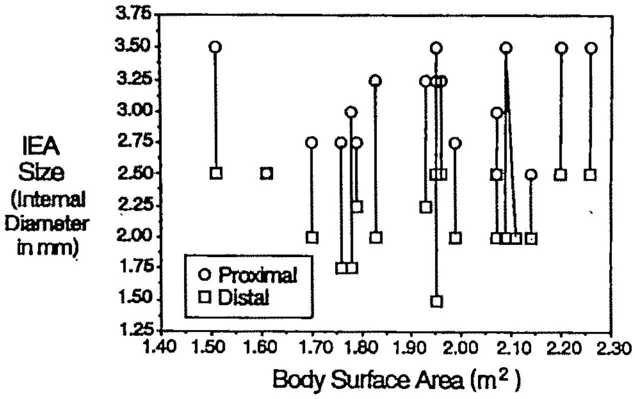


Fig 12. Proximal and distal sizes of 17 inferior epigastric arteries (IEAs) matched to body surface area in patients after dilute papaverine preparation of their grafts.

iliac atherosclerosis that extended into the first few millimeters of their IEAs.

Postoperative follow-up has been from 1 to 18 months. There have been no deaths. One patient had a sterile hematoma that evacuated spontaneously from the rectus paramedian incision. In another patient, a 224-kg, 1.68-m diabetic woman, a late wound infection developed after hospitalization. Since that time Jackson-Pratt drains have been used, and no further postoperative wound complications have occurred. The average amount of blood retrieved by the Jackson-Pratt drains has been less than 75 mL. There have been no hernias. We have not detected any evidence of rectus muscle necrosis secondary to interruption of the blood supply to that muscle. No motor dysfunction of that muscle has been noted.

Comment

The IEA offers an alternative as a bypass graft, although its dissection is more time consuming. It is especially useful in patients in whom it is difficult to harvest enough conduit and for young patients with a projected substantial longevity. Long-term patency of this graft remains in question; however, there is some indirect evidence that it may indeed offer patency similar to the free IMA graft [5]. Thirteen of our 18 patients had ipsilateral harvest of their IMAs. The potential complication of rectus necrosis has not been observed in our series and to our knowledge has not been reported. It is our opinion that to avoid this complication it is important to substantially limit circumferential dissection of the rectus muscle. The theoretical complication of infertility in a young man with inadvertent injury to the spermatic duct should be discussed with patients in that age group before bilateral harvest of IEAs. Testicular necrosis secondary to ligation of the external spermatic artery is a theoretical, yet unreported complication. The dissection is extraperitoneal; therefore, intraabdominal complications should be nil. Injury to the genitofemoral nerve is a potential complication with bleeding and difficult exposure in an obese patient at the site of origin of the IEA. We have not found it necessary to use vein or other material at the proximal anastomosis. Theoretically the use of vein in itself defeats the purpose of using an arterial conduit.

Three patients who have had postoperative angiography had widely patent IEAs within 10 days of operation. Two had proximal anastomoses to the aorta (1 with a natural Y IEA), and one proximal anastomosis was to the left IMA. Previous authors have stressed the importance of short-term physiological studies and long-term angiographic follow-up to determine the true efficacy of this conduit.

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Risk Factors for Nosocomial Pneumonia After Coronary Artery Bypass Graft Operations

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We attempted to determine risk factors for nosocomial pneumonia in patients undergoing a coronary artery bypass graft operation. We reviewed the microbiology and medical records for any patient with a sputum culture who had undergone a coronary artery bypass graft operation in 1988 to identify patients with pneumonia according to a standard clinical definition. We found 19 cases of pneumonia through our initial review; complete medical records were found on 15 cases. Gram-negative bacilli predominated as the most common etiologic agent causing pneumonia in this cohort. There were no clusters noted. Mortality was 26.6%. Pneumonia occurred approximately 4 days after the operation. Thirty-six controls were randomly selected from patients undergoing coronary artery bypass graft operations in 1988. Logistic regression analysis revealed that a history of chronic obstructive lung disease, duration of more than 2 days of mechanical ventilation after operation but before diagnosis of pneumonia, and receipt of gastric acid inhibitors (antacids or H_2-blockers) were independent risk factors for nosocomial pneumonia. Only the last risk factor was amenable to intervention at the time of operation.

(Ann Thorac Surg 1991;51:215–8)

Despite recent advances in medical treatment, nosocomial pneumonia remains one of the most serious of all hospital-acquired infections. It is the second most common of all hospital-acquired infections [1]. Hospital-acquired pneumonia develops in 10% to 70% of patients requiring mechanical ventilation [2–7]. In one study [8] nosocomial pneumonia was the most common site of infection in patients who died with nosocomial infections with a case-fatality rate of 60%. High case-fatality rates have been noted in other studies as well [4, 7, 9, 10, 11]. When compared with all other hospital-acquired infections, nosocomial pneumonias also pose the greatest expense to hospitals owing to their excessive length of stay and the cost of treatment [12].

Several factors contribute to the high mortality rate of nosocomial pneumonia. The presence of certain underlying conditions such as hypotension, chronic obstructive pulmonary disease, advanced age, endotracheal intubation, operation (especially high abdominal or thoracic), and congestive heart failure have been associated with high fatality rates from nosocomial pneumonia [3, 7, 8, 13]. Many if not all of these risk factors may be present in a patient undergoing coronary artery bypass graft (CABG) operations. The purpose of this study is to determine risk factors for nosocomial pneumonia in patients undergoing CABG operations.

For editorial comment, see page 177.

The University of Michigan Hospitals and Medical Center is an 888-bed tertiary-care hospital. Approximately 425 CABG operations are performed each year. The thoracic intensive care unit is located in the University Hospital and is a 10-bed facility for patients undergoing the spectrum of adult cardiac surgical procedures.

Patients undergoing CABG operation are usually admitted 1 day preoperatively. All of the patients are admitted directly to the thoracic intensive care unit from the operating room/recovery room.

Material and Methods

Case Definition

We examined charts of patients undergoing CABG operations in 1988 at the University of Michigan Hospitals who (1) had a chest roentgenogram that showed a new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion and (2) had at least one of the following: new, purulent sputum, organism isolated from a blood culture, or isolation of an etiologic agent from a respiratory specimen [14].

Descriptive Epidemiology

We reviewed the microbiology records for any patient with a sputum culture from the Cardiac Surgery Service in 1988. The charts of patients who had undergone CABG operations were then reviewed to identify patients with pneumonia according to the above definition.

We reviewed case-charts for factors including age, sex, height, weight, underlying disease (diabetes, congestive heart failure, chronic obstructive pulmonary disease), other postoperative infections, pack-years of smoking, smoking 2 weeks before operation, reoperation for bleed-

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ing, postoperative hypotension (systolic blood pressure < 90 mm Hg), antibiotic prophylaxis, type of operation (emergency versus elective), duration of operation, date of onset of infection, organism, presence of secondary bacteremia, antimicrobial susceptibility of the organism, antibiotic use (preoperative and postoperative), ventilator-days before diagnosis of pneumonia, length of preoperative stay, steroid or other immunosuppressive drug use, surgical staff exposures, creatinine level greater than 180 μmol/L (2 mg/dL) postoperatively, albumin level less than 30 g/L (3g/dL) postoperatively, difficulty of intubation, receipt of gastric acid inhibitor(s) (antacids or H_2-blocker) versus sucralfate, prolonged obtundation postoperatively (>24 hours after operation), and type of preoperative and postoperative respiratory therapy.

Analytical Epidemiology

We performed a case-control study to determine the risk factors associated with nosocomial pneumonia in this patient population. Controls were randomly selected from patients undergoing CABG operations during 1988. After excluding cases, patients undergoing CABG operations during 1988 were numbered; two controls were selected for each case using a table of random numbers. Two controls were excluded because they met part but not all of the case definition. The control-patient charts were reviewed for the same factors as the cases, as appropriate. Statistical analyses were performed with the χ^2 test or the t test, where appropriate [15]. Logistic regression analysis was also used [15].

Results

Descriptive Epidemiology

Nineteen patients (3.8%) met the case definition out of 498 patients undergoing CABG operations in 1988. Pneumonia occurred an average of 3.67 (± 4.2) days postoperatively. Mortality was 26.6% but none of the patients had an autopsy to confirm pathological findings. All patients had purulent sputum; all sputum specimens except one were recovered from an endotracheal suction. Five patients had a positive blood culture with the same organism found in the sputum. Two patients suffered from second episodes of pneumonia with organisms that differed from their first episodes. The vast majority of organisms isolated were gram-negative bacilli: *Pseudomonas aeruginosa*, 3; *Enterobacter aerogenes*, 3; *Xanthomonas maltophilia*, 2; *Haemophilus influenzae*, 2; *Klebsiella pneumoniae*, 2; *Klebsiella oxytoca*, 1; *Enterobacter cloacae*, 1; *Serratia marcescens*, 1; and *Citrobacter freundii*, 1. Seven patients had gram-positive cocci (*Staphylococcus aureus*, 5; coagulase-negative staphylococci, 2), and 4 had fungi (*Candida albicans*, 3; *Aspergillus fumigatus*, 1). A total of 27 organisms were isolated among 15 nosocomial pneumonias after CABG operations for which complete medical records were available. No cluster of pneumonia episodes or organisms was noted.

Complete records could not be obtained on 4 patients, and they were excluded from further analysis. Five (33%) of the 15 patients for whom complete records could be obtained had a secondary bacteremia. Four of 15 patients had infections at other sites in the postoperative period before diagnosis of pneumonia. Only 4 of 15 had hypotension in the immediate postoperative period; 3 patients had smoked in the 2 weeks before CABG operation. Only 1 of the patients had undergone an emergency operation.

Table 1. Case-Control Study Analysis of Nosocomial Pneumonia After Coronary Artery Bypass Graft Operations

Variable	Cases (n = 15)	Controls (n = 36)	p Value[a]
Sex (male)	12	27	NS
Age (average; y)	62.1	62.5	NS[b]
Antibiotic prophylaxis			
Vancomycin	2	11	NS
Cefazolin	10	24	
Other	3	1	
History of COPD	7	3	0.001
Receipt of gastric acid inhibitors	12	15	0.01
Other nosocomial infections	4	3	NS
Pack-years of smoking	39.8	35.1	NS
Duration of operation (average; min)	319.3	273.2	NS[b]
Duration of intubation[c]	139.9	40.1	<0.001[b]
CHF	7	3	0.001

[a] χ^2 test, one-tailed [15]. [b] t test [15]. [c] Duration of intubation = hours of intubation postoperatively before diagnosis of pneumonia for cases and hours of intubation for the entire postoperative period for controls.

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; NS = not significant.

Analytical Epidemiology

The analysis of the case-control study is summarized in Table 1. The cases and controls were similar with respect to underlying diseases, sex, and age. No control patients died. No significant differences were noted for operating room location or perioperative antibiotic prophylaxis. However, in a univariate analysis, cases differed from controls in that cases more often had a history of chronic obstructive pulmonary disease or congestive heart failure. Finally, cases had received either antacids or H_2-blockers (rather than sucralfate) more often than controls; only 1 control patient had received both antacids and sucralfate.

Logistic regression analysis is shown in Table 2. Of the factors that were significantly different between cases and controls, only three were independently important in the logistic regression modelling: history of chronic obstructive pulmonary disease, receipt of gastric acid inhibitor, and days on a ventilator before diagnosis of pneumonia.

Comment

Our study suggests that nosocomial pneumonia occurred in approximately 4% of our patients undergoing CABG

Table 2. Stepwise Logistic Regression Analysis of Case-Control Study Analysis of Nosocomial Pneumonia After Coronary Artery Bypass Graft Operations

Model No.	Risk Factor	Log Likelihood at MLE	p Value
1	History of COPD	37.8205	0.0296
2	History of COPD, duration of intubation (>48 hours)[a]	35.5432	<0.0001
3	History of COPD, duration of intubation (>48 hours)[a], gastric acid inhibitor	19.4439	<0.00001

[a] Duration of intubation = hours of intubation postoperatively before diagnosis of pneumonia for cases and hours of intubation for the entire postoperative period for controls.

COPD = chronic obstructive pulmonary disease; MLE = maximum likelihood estimate.

operations. As in other studies, gram-negative bacilli were the predominant etiologic agents causing pneumonia [1–3, 7, 10, 13, 16]. Despite this predominance, the case-fatality rate was 26.6%, which was lower than that of most other reported studies of pneumonia with gram-negative pneumonia [4, 7, 9, 10, 16].

Risk factors that were independently associated with pneumonia—a history of chronic obstructive pulmonary disease, receipt of gastric acid inhibitors, and a long duration of mechanical ventilatory support before diagnosis of pneumonia—have been described in previous studies [2–7, 13, 16, 17]. In this cohort of patients, although the prevalence of congestive heart failure was significantly different between cases and controls in the univariate analysis, logistic regression did not reveal this risk factor to be independently associated with nosocomial pneumonia. Our study must be interpreted with caution, however. The complete medical records on 4 patients with pneumonia and 2 control patients were unavailable and may have introduced important bias in the study. Our case definition, although consistent with that of the Centers for Disease Control [14], may have included or excluded cases of pneumonia. Exclusions may be especially important because 2 control patients were excluded as they met a portion of the case definition. However, the remainder of the control patients had no evidence of consolidation on physical examination or infiltrates on chest roentgenogram.

Of the risk factors found in this study, only receipt of gastric acid inhibitors is amenable to intervention at the time of operation. Sucralfate's efficacy to prevent bleeding from stress ulcers is similar to that of H_2-blockers [18–21]. We confirmed the findings of another study that suggested that H_2-blockers are a risk factor for nosocomial pneumonia [17]. Although the mechanism of "protection" is thought to be maintenance of low gastric pH and its resultant effects on bacterial growth [17], one report suggest that sucralfate may have a direct antibacterial effect on gram-negative bacilli [22]. Sucralfate is now used exclusively in our thoracic intensive care unit after CABG operations for prevention of gastric stress ulcers.

If others confirm our findings, the risk factors for nosocomial pneumonia after CABG operations may serve to identify a group at high risk for pneumonia, who would be eligible for newer interventions such as selective digestive tract decontamination [23, 24].

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Dr Richard M. Peters, who has functioned as an Associate Editor in charge of book reviews for the past 11 years, at his request retired from this position at the time of the Interim Meeting of The Society of Thoracic Surgeons in Chicago, September 21, 1990. He will remain as an Editorial Board member. Dr Peters has performed a great service for the readers of *The Annals*, and we are grateful to him.

Dr J. Kent Trinkle has agreed to be the new Associate Editor in charge of book reviews. Any correspondence concerning this section of *The Annals* should be sent directly to him at the address listed below:

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Response to Chemotherapy Does Not Predict Survival After Resection of Sarcomatous Pulmonary Metastases

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Between 1979 and 1988, 26 patients with pulmonary metastases from adult soft-tissue sarcomas were treated with Adriamycin (doxorubicin hydrochloride), Cytoxan (cyclophosphamide), and DTIC before metastasectomy. Thirty-eight thoracotomies were performed with postoperative complications in 5 patients (5/38, 13.2%) and one postoperative death (1/38, 2.6%). Two patients had benign lesions at thoracotomy and were excluded from further survival analysis. The median survival of the remaining 24 patients after thoracotomy was 18.5 ± 5.9 months, and the actuarial 5-year survival was 22%. Five patients (5/24, 21%) achieved a clinically complete response with preoperative chemotherapy, but all had recurrence in the lung and underwent resection of pulmonary metastases. Seven patients (7/24, 29%) achieved a partial response and had residual disease resected at thoracotomy. Twelve patients (12/24, 50%) showed either no change or disease progression while receiving chemotherapy and were referred for resection. Postthoracotomy disease-free survival and postthoracotomy overall survival did not differ significantly between the three groups. One patient in the group showing no change or progression of disease while receiving chemotherapy is alive without recurrence 57 months after initial pulmonary metastasectomy. Chemotherapy can be used for the initial treatment of pulmonary metastases from adult soft-tissue sarcomas. However, survival after resection of pulmonary metastases cannot be accurately predicted based on the clinical response to preoperative chemotherapy.

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The efficacy of resection of isolated pulmonary metastases in patients with soft-tissue sarcomas is well established [1–3]. Favorable prognostic factors include fewer than five pulmonary nodules on preoperative computed tomographic scans or linear tomograms, a tumor doubling time of greater than 20 days, and a preoperative disease-free interval of greater than 12 months [4–7]. Although combination chemotherapy produces significant responses in many patients with metastatic soft-tissue sarcoma [8–11], few patients with metastatic disease achieve long-term survival with chemotherapy alone. Rosenberg and colleagues [12] reported improved survival in patients with extremity soft-tissue sarcomas treated with adjuvant Adriamycin (doxorubicin hydrochloride) and Cytoxan (cyclophosphamide) after complete resection of the primary sarcoma. Others [13], however, have failed to show a beneficial effect in this setting.

In patients with metastatic soft-tissue sarcoma, a favorable response to chemotherapy administered before pulmonary metastasectomy may be predictive of prolonged survival after surgical resection of pulmonary metastatic disease. This study examines survival in patients with sarcomatous pulmonary metastases treated with preoperative chemotherapy followed by pulmonary metastasectomy. In this select population, the preoperative response to chemotherapy was not predictive of overall survival or disease-free survival after pulmonary resection.

Material and Methods

Patient Population

Between 1979 and 1988, 26 patients were retrospectively identified after treatment at The University of Texas MD Anderson Cancer Center. These patients were treated with combination chemotherapy followed by exploration and resection of pulmonary metastases, had a histologically confirmed diagnosis of soft-tissue sarcoma, had the primary tumor controlled, and had metastatic disease that was confined to the thorax and was deemed potentially resectable. All patients were part of a prospective study designed (1) to evaluate the efficacy of combination chemotherapy with single-dose cyclophosphamide and 4-day infusion of Adriamycin and dimethyltriazeno-imidazole-carboxamide (DTIC) in the treatment of patients with metastatic or inoperable soft-tissue sarcomas and (2) to maximize tumor reduction by surgical excision.

There were 13 male and 13 female patients with a mean age of 40 years (range, 17 to 68 years). The mean follow-up after initial resection was 75 months (range, 42 to 109 months). Thirteen patients (13/26, 50%) had primary tumors of the extremities, 9 patients (9/26, 35%) had

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truncal sarcomas, and 4 patients (4/26, 15%) had primary sarcomas of the retroperitoneum.

All patients received combination chemotherapy preoperatively for two to 16 cycles (mean number, six cycles). Chemotherapy consisted of Adriamycin (60 mg/m^2 infused over 96 hours), Cytoxan (600 mg/m^2), and DTIC (1 g/m^2 over 96 hours). Two patients also received vincristine sulfate. Combination chemotherapy was continued postoperatively unless toxicity was prohibitive.

Patients were stratified to one of three response categories according to standard response criteria as judged by the attending physician's evaluation of clinical response at the time of treatment: CR = complete response, no measurable disease; PR = partial response, greater than 50% reduction in volume of measurable disease; NC = no change or less than 50% reduction in volume of measurable disease; and PRO = progressive disease. Twelve patients (12/26, 46%) whose disease either showed no clinically significant change (NC) or progressed (PRO) while they were receiving chemotherapy were classified as NC/PRO. Five patients (5/26, 19%) who achieved a clinically complete response with chemotherapy (not pathologically confirmed) but later had recurrence (RE) and underwent metastasectomy were classified as CR/RE. Seven patients (7/26, 27%) whose disease partially regressed with chemotherapy and who had residual disease resected were classified as PR.

Patients undergoing thoracotomy met previously described criteria [4]. Briefly, the primary tumor was controlled, extrapulmonary metastases were absent, and the lesions were considered resectable. Thoracic exploration was performed through a median sternotomy or staged bilateral thoracotomies as previously described [14]. All gross disease was removed when technically possible, sparing maximal pulmonary parenchyma.

Statistical Analysis

Postoperative survival and disease-free survival were estimated using the product-limit method of Kaplan and Meier [15]. Statistical comparisons between groups were made using the log-rank test with survival estimated from the time of pulmonary metastasectomy. All p values reported are two tailed.

Results

The 26 patients had a total of 37 thoracotomies. Seventeen patients (17/26, 65%) underwent a single exploration, 7 patients (7/26, 27%) underwent two explorations, 1 patient (1/26, 4%) underwent three explorations, and 1 patient (1/26, 4%) underwent four explorations. Postoperative complications occurred in 5 patients (5/38, 13.2%): air leaks for longer than 7 days (n = 3), bleeding necessitating transfusion (n = 1), and postoperative myocardial infarction (n = 1). One patient (1/38, 2.6%) died 3 days after the fourth thoracotomy for a pulmonary metastasis invading the mediastinum. A portion of esophagus was resected, and the patient subsequently died of sepsis. Postmortem examination was not performed. Chemotherapy-related toxicity necessitating dose reduction developed in 11 patients (11/26, 42%). One patient who received high-dose Adriamycin died (disease free) of congestive heart failure 45 months after thoracotomy.

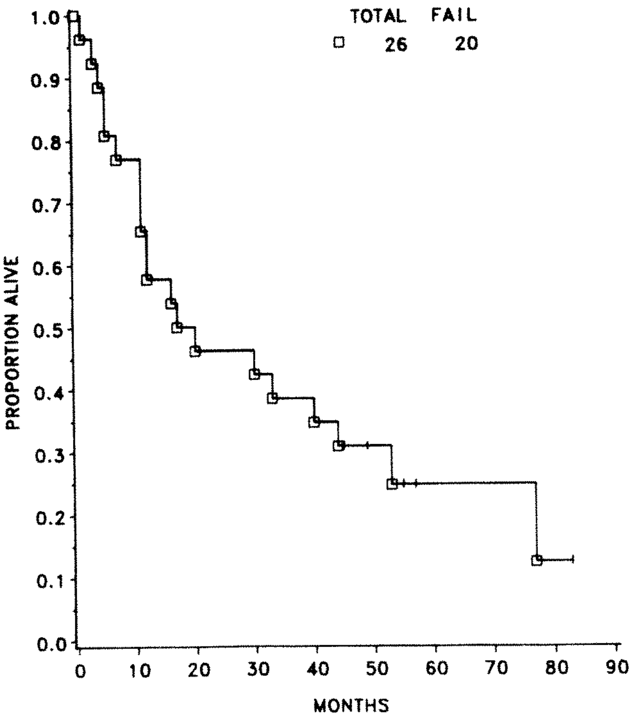

Fig 1. Overall actuarial survival of all patients after thoracotomy (n = 26).

After thoracotomy, the median survival of the entire cohort of 26 patients was 18 ± 5.8 months, and the actuarial 5-year survival was 24.6% (Fig 1). Two (8%) of the 26 patients were found to have fungal lesions (cryptococcosis, 1; histoplasmosis, 1) at thoracotomy and were excluded from further survival analysis. The remaining 24 patients with histologically confirmed pulmonary metastases had a postthoracotomy median survival of 18.5 ± 5.9 months and an actuarial 5-year survival of 22%. Three patients (3/24, 12.5%) could not be made disease free at operation because of hilar node involvement with sarcoma (n = 1), miliary sarcomatous metastases (n = 1), or myocardial infarction after the first of staged thoracotomies for bilateral metastases (n = 1). None of the 3 patients was alive at 12 months after thoracotomy despite aggressive additional treatment. In contrast, the median survival of the 21 patients rendered disease free was 30 ± 6.4 months, and the actuarial 5-year survival was 25% ($p = 0.0053$) (Fig 2).

Five patients with histologically proven metastatic disease (5/24, 21%) achieved a clinically complete response with preoperative chemotherapy alone (CR/RE group) (Tables 1, 2). However, none of these patients were explored to confirm histological response to chemotherapy. They received a mean of 13 cycles (range, 2 to 16 cycles) of preoperative chemotherapy. All 5 patients had recurrence in the lungs 4 to 57 months (mean time, 20.8 months) after achievement of complete response and

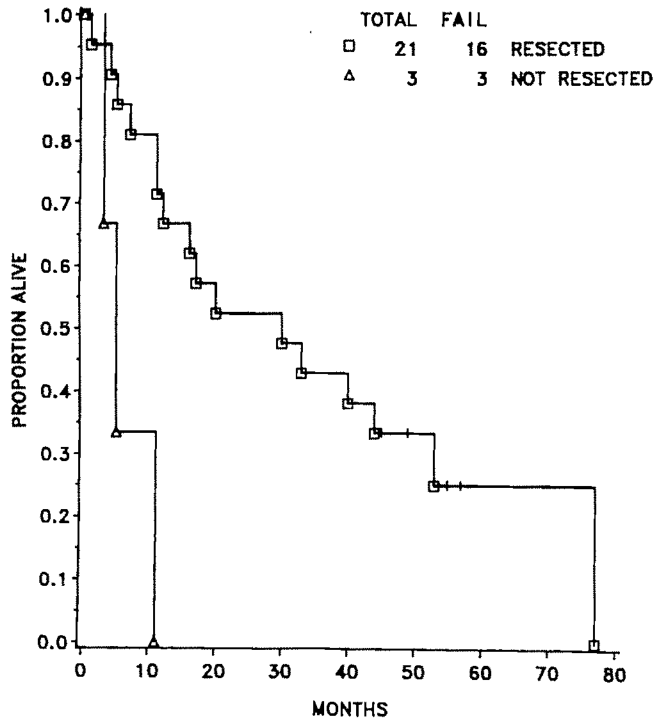

Fig 2. Overall postthoracotomy actuarial survival of all patients with histologically proven pulmonary metastases by resectability at thoracotomy (n = 24) (p = 0.0053).

were then referred for resection. The mean number of malignant nodules resected was 2.4 (range, 1 to 7). One patient could not be made disease free at operation because of a postoperative myocardial infarction after the first of staged thoracotomies for bilateral disease. This patient died 11 months after thoracotomy. The postthoracotomy median survival of the remaining 4 patients made disease free at operation was 36.5 ± 11.6 months, and the postthoracotomy median disease-free survival was 7.5 ± 1.7 months. None of the 5 patients in this group were alive at 5 years after thoracotomy. Three died of progressive pulmonary metastases, and 1 died (clinically disease free) of congestive heart failure at 45 months after thoracotomy.

Seven of the 24 patients with histologically proven metastatic disease (7/24, 29%) achieved a partial response after preoperative chemotherapy (PR group) (see Tables 1, 2). The mean number of preoperative chemotherapy cycles in this group was eight (range, 4 to 18). The patients then underwent thoracotomy for resection of residual disease. The mean number of malignant nodules resected was 3 (range, 1 to 12). All patients were made disease free at thoracotomy. The postthoracotomy median survival of this group was 40 ± 12.1 months, and the postthoracotomy median disease-free survival was 11 ± 2.6 months. All 7 patients had recurrence after thoracotomy, and 5 of the 7 died of progressive metastases. One surviving patient remains disease free 49 months after a second thoracotomy to resect recurrent disease. The other surviving patient is alive with documented disease recurrence 45 months after the first thoracotomy.

Twelve patients with histologically proven metastases (12/24, 50%) experienced either no clinically apparent change (n = 4) or disease progression (n = 8) while receiving chemotherapy (NC/PRO group) (see Tables 1, 2). These patients received a mean of 3.6 cycles (range, 2 to 7) of preoperative chemotherapy. The mean number of malignant nodules resected at thoracotomy in this group was 4.7 (range, 1 to 12). Two patients could not be made disease free at thoracotomy because of hilar involvement with sarcoma (n = 1) or miliary metastases (n = 1). These 2 patients died 5 months and 3 months after thoracotomy, respectively, despite additional treatment. The postthoracotomy median survival of the remaining 10 patients was 16.5 ± 5.6 months, and the postthoracotomy median disease-free survival was 6.5 ± 3 months. A single patient has not had recurrence after the initial thoracotomy and remains disease free at 57 months. A second patient remains alive with disease at 55 months after the initial thoracotomy. All other patients in this group (10/12, 83%) died of progressive metastases.

Postthoracotomy disease-free survival did not differ between the three patient groups (p = 0.783) (Fig 3). Similarly, no significant differences were found in postthoracotomy actuarial survival between groups (p = 0.533) (Fig 4) despite complete surgical resection of metastatic disease.

Comment

Tumor response to preoperative chemotherapy in patients with primary soft-tissue sarcomas may provide a biological assessment of tumor sensitivity to chemotherapeutic agents and indirectly predict survival. However, the clinical response to preoperative chemotherapy for pulmonary metastases from soft-tissue sarcomas in this select patient population was not indicative of survival after thoracotomy. In osteosarcomas, histological evidence of a response to preoperative chemotherapy, measured as percent tumor necrosis, has been found to be a significant prognostic factor [16]. This information has been used to modify the treatment regimens of poorly responding patients [17]. Similarly, patients with squamous cell carcinoma of the esophagus who show a response to preoperative chemotherapy have been found to have prolonged survival compared with nonresponders or controls in a prospective randomized trial [18].

Surgical resection of pulmonary metastases in patients with soft-tissue sarcomas provides improved postthoracotomy survival [1, 4, 7, 19]. Despite complete resection, the majority of patients with pulmonary metastases from soft-tissue sarcomas will have recurrences in the lung, and many die of progressive pulmonary insufficiency. The development of combination chemotherapy with marked activity against soft-tissue sarcomas has improved overall survival in patients with disseminated disease [20, 21].

The incidence of postoperative complications in this patient population (13.2% morbidity and 2.6% mortality) compares favorably with that in another reported series

Table 1. Effect of Preoperative Chemotherapy Response on Postthoracotomy Survival of Patients With Adult Soft-Tissue Sarcomas[a]

Patient No.	Age (y)	Sex	No. of Preop Chemotherapy Cycles	Response	Resectable	No. of Nodules	Postthoracotomy Overall Survival (mo)	Postthoracotomy Disease-Free Survival (mo)
1	23	M	15	CR/RE	Yes	1	20	20
2	61	M	15	CR/RE	Yes	1	(45)	(45)
3	39	M	10	CR/RE	Yes	1	11	6
4	38	F	16	CR/RE	Yes	7	53	9
5	62	F	10	CR/RE	No	2	11	0[b]
6	41	M	18	PR	Yes	2	(49)[c]	9
7	60	M	4	PR	Yes	3	7	4
8	57	F	8	PR	Yes	1	12	9
9	60	F	7	PR	Yes	1	40	11
10	48	F	4	PR	Yes	12	77	26
11	20	F	5	PR	Yes	1	33	12
12	58	M	7	PR	Yes	1	(45)[d]	12
13	49	M	2	PRO	Yes	3	44	26
14	17	M	3	PRO	Yes	5	17	5
15	53	F	6	PRO	Yes	10	16	3
16	25	M	3	PRO	No	. . .	3	0
17	37	F	2	PRO	Yes	4	4	1
18	17	M	3	PRO	Yes	1	1	1
19	40	F	7	PRO	No	. . .	5	0
20	47	F	2	PRO	Yes	4	5	1
21	68	M	2	NC	Yes	1	(57)[e]	(57)
22	34	M	3	NC	Yes	2	11	11
23	54	F	3	NC	Yes	12	(55)[d]	8
24	52	M	7	NC	Yes	5	30	10
25	47	M	10	NC	. . .	0[f]	12	. . .
26	66	F	3	NC	. . .	0[f]	(83)	(83)

[a] Parentheses denote censored observation. [b] Second of staged thoracotomies was not done because of a myocardial infarction. [c] Patient is alive with no evidence of disease after second resection. [d] Patient is alive with disease after first resection. [e] Patient is alive with no evidence of disease after first resection. [f] Fungal disease only was found at thoracotomy.

CR/RE = complete response/recurrence; NC = no change; PR = partial regression; PRO = progression.

[4] of similar patients not receiving preoperative chemotherapy. Chemotherapy as described can be safely administered preoperatively in this patient population without significantly increasing perioperative risks.

Few reports have examined the effect of preoperative chemotherapy on postoperative survival after resection of sarcomatous pulmonary metastases. Huth and associates [22] reviewed the outcome of 43 patients with sarcomas of

Table 2. Effect of Preoperative Chemotherapy Response on Postthoracotomy Survival of Patients With Malignant Histology Made Disease Free at Thoracotomy

Group	No. of Patients	Mean No. of Preop Chemotherapy Cycles	Mean No. of Malignant Nodules Resected	Postthoracotomy Median Survival[a] (mo)	Postthoracotomy Median Disease-Free Survival[b] (mo)	Actuarial 36-Month Survival (%)	Status
CR/RE	4	14	2.5	36.5 ± 11.6	7.5 ± 1.7	50	3 DWD; 1 DNED
PR	7	8	3	40.0 ± 12.1	11.0 ± 2.6	57	1 NED; 1 AWD; 5 DWD
NC/PRO	10	3.3	4.7	16.5 ± 5.6	6.5 ± 3.0	30	1 NED/NR[c]; 1 AWD; 8 DWD

[a] Significance: $p = 0.533$. [b] Significance: $p = 0.783$. [c] This is the only patient alive without recurrence after the initial thoracotomy 57 months ago.

AWD = alive with disease; CR/RE = complete response/recurrence; DNED = dead, no evidence of disease; DWD = dead with disease; NC/PRO = no change/progression; NED = no evidence of disease; NR = no recurrence; PR = partial regression.

various histologies who underwent pulmonary metastasectomy including 20 patients with osteosarcoma (20/43; 46.5%). Twenty-one patients (21/43; 49%) received preoperative chemotherapy (histologies not given) and were retrospectively stratified by response. All 5 patients who demonstrated a clinical response were alive without disease a median of 23 months postoperatively. Ten patients had prolongation of the tumor doubling time to greater than 40 days. The median survival of these patients was 24 months. Six patients showed no response to chemotherapy, and their postthoracotomy median survival was only 11.5 months. In this study, changes in tumor growth induced by preoperative chemotherapy favorably affected survival after metastasectomy.

The histologies of the subset of 21 patients who received preoperative chemotherapy were not stated and may have included histologies other than soft-tissue sarcomas. In addition, the chemotherapy protocol differed substantially from that administered to our patient population. The effects and outcome of these two differences are difficult to determine.

Giritsky and co-workers [23] examined the effect of preoperative chemotherapy on survival of 12 pediatric patients with metastatic osteogenic sarcoma. These patients received intensive preoperative chemotherapy and preoperative or postoperative pulmonary irradiation before pulmonary metastasectomy. Three-year survival was 57.8% and compares favorably with that of other reported series. The value of preoperative chemotherapy, pulmonary metastasectomy, and possibly pulmonary irradiation in patients with pulmonary metastases from osteogenic sarcoma is unclear, as the results were based on comparison with historical controls and can be considered only tentative.

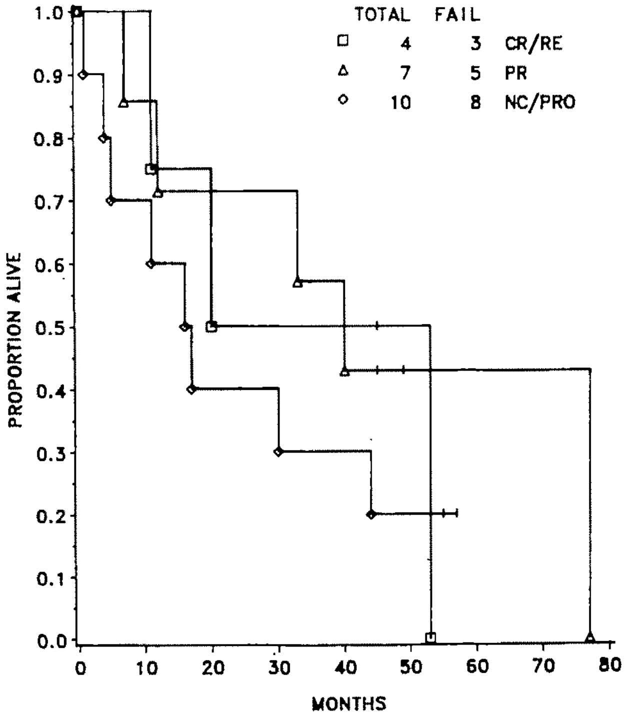

Fig 3. Overall postthoracotomy disease-free survival of all patients with malignant histology who were made to have no evidence of disease at thoracotomy (n = 21) (p = 0.783). (CR/RE = complete response to chemotherapy/recurrence; NC/PRO = no change/progression while on chemotherapy; PR = partial regression with chemotherapy.)

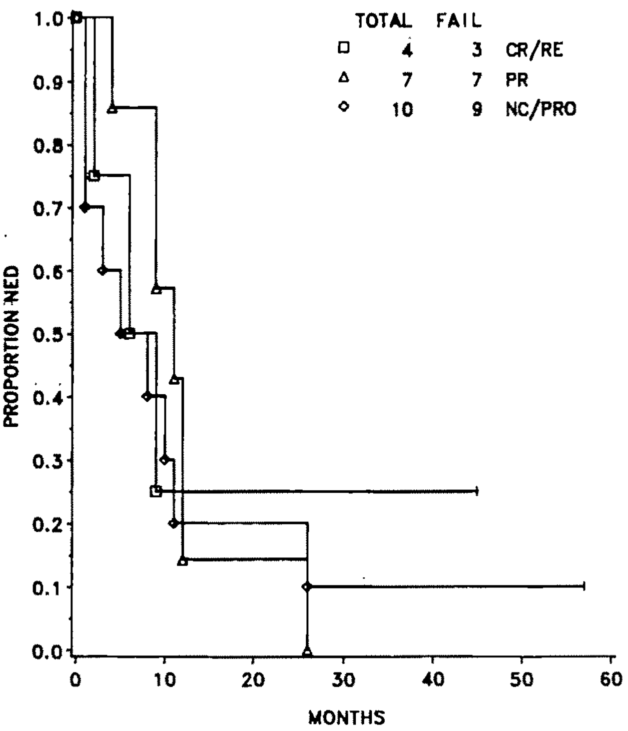

Fig 4. Overall postthoracotomy actuarial survival of all patients with malignant histology who were made to have no evidence of disease at thoracotomy (n = 21) (p = 0.533). (CR/RE = complete response to chemotherapy/recurrence; NC/PRO = no change/progression while on chemotherapy; PR = partial regression with chemotherapy.)

Belli and colleagues [24] observed only one complete response, one partial response, and three disease stabilizations among 24 patients with osteosarcoma metastatic to the lungs who were treated with combination chemotherapy before metastasectomy. All patients had received previous chemotherapy during treatment of the primary tumor. In this review, the clinical response to bulk disease in patients who had received previous chemotherapy was poor. A survival advantage was not observed for the responding patients.

In our patients, the response to preoperative chemotherapy was not a reliable predictor of postthoracotomy survival. Mutational models for the development of drug resistance predict that an inverse relationship exists between curability and tumor burden [25]. Thus, the earliest possible use of appropriate chemotherapy may have the potential for improving cure rates for solid tumors. Most patients in this series who responded to chemotherapy received prolonged courses of chemotherapy before operation. Surgical intervention was undertaken only when there was evidence of disease recurrence or progression or when a complete response could not be achieved. We are now evaluating a short course of preoperative chemotherapy (two or three cycles) followed by additional chemotherapy after resection. The response to preoperative chemotherapy has proved to be a useful prognostic indicator in other solid tumors [16, 18]. The clinical response to chemotherapy represents complex interactions between malignant cell subsets and cytotoxic agents. Disparate responses have been noted between the primary tumor and its metastases in patients receiving preoperative chemotherapy [26]. Thus, the clinical response to chemotherapy given preoperatively may not reliably predict survival outcome in all histologies, as micrometastases may respond differently than bulk disease. Further studies will be helpful in defining these complex interactions.

Two of the 26 patients were found to have unresectable metastases at thoracotomy. Both were in the NC/PRO group. The usefulness of preoperative chemotherapy in improving resectability or survival could not be determined from our data.

In conclusion, preoperative chemotherapy can be used safely in patients with pulmonary metastases from soft-tissue sarcomas. A high clinical response rate can be achieved in this population using chemotherapy combinations that include Adriamycin, Cytoxan, and DTIC. However, the clinical response to preoperative chemotherapy cannot be used to accurately predict overall survival or disease-free survival after complete surgical resection of metastatic disease. Aggressive surgical resection of metastatic disease in patients with pulmonary metastases from soft-tissue sarcomas can result in long-term survival and should be performed for all patients with potentially resectable pulmonary metastases regardless of response to preoperative chemotherapy.

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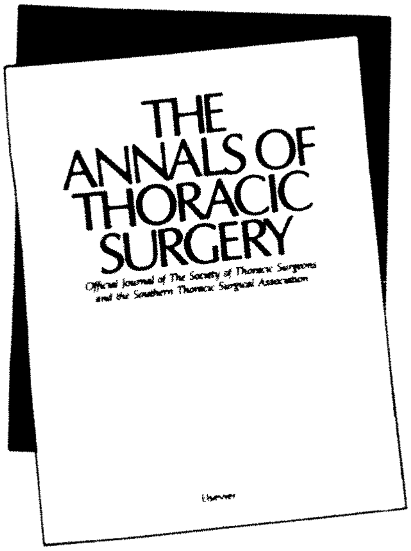
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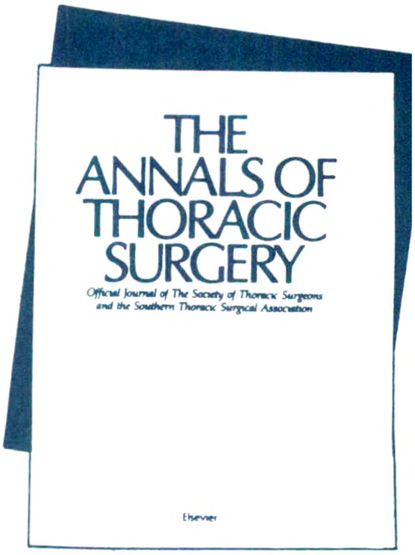
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Electrocautery Does Not Interfere With the Function of the Automatic Implantable Cardioverter Defibrillator

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The automatic implantable cardioverter defibrillator (AICD) manufactured by Cardiac Pacemakers, Inc, contains an automatic sensitivity adjustment. We tested whether this feature would prevent sensing of signals generated by electrocautery by implanting three different models of the AICD in 4 mongrel dogs. Unipolar electrocautery was applied at maximum output to a site close to the rate-sensing leads. The devices were monitored with an AICD-check probe and by auditory monitoring of QRS synchronous tones. No sensing of the electrocautery by the device occurred. Three patients with two different AICD models (1550 and 1520) underwent five surgical procedures in which electrocautery was used. No sensing of electrocautery signals, device charging, or other device malfunction occurred.

(Ann Thorac Surg 1991;51:225–6)

The manufacturer of the only automatic implantable cardioverter defibrillator (AICD) available outside of clinical trials, Cardiac Pacemakers, Inc (CPI), St. Paul, MN, currently recommends that these devices be deactivated before surgical procedures in which electrocautery will be used [1, 2]. This recommendation is made because of concerns that electrocautery could provide signals that the device might interpret as QRS complexes and fire inappropriately. Oversensing and other device/cautery interactions with pacemakers are well known [3].

Previous and current models of the CPI AICD contain an automatic gain control, which adjusts the sensitivity according to the size of the epicardial or intracardiac electrograms detected by the rate-sensing leads. We thought it unlikely that electrocautery would cause oversensing in the presence of an adequate electrogram, which would keep the sensitivity low. To test this hypothesis, we implanted three different models of the CPI AICD into 5 mongrel dogs through a thoracotomy and applied electrocautery at maximal outputs to the margins of the thoracotomy incision.

Material and Methods

Experimental Trials

Three different models of the CPI AICD (1500, 1510, and 1520) were implanted in 5 dogs. The 1500 was implanted in all 5 dogs; the 1510 and 1520 were implanted in 3 dogs. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Devices were implanted both with and without the defibrillating leads in place. Models 1500 and 1510 had the probability density function; model 1520 did not. The only difference between the 1500 and the 1510 is the first defibrillation shock energy, which is 25 J in the 1500 and 30 J in the 1510.

The devices were implanted through a large thoracotomy incision with the dogs under general anesthesia. Model 431 CPI epicardial screw-in leads were used for rate sensing and, under direct vision, were screwed into the epicardium. Defibrillating and morphology-sensing leads were placed around the heart by slipping them between the epicardium and pericardium. The leads were then attached to the AICD. The device was either left in an external position or placed in the chest incision. In 3 dogs, R waves were measured through the rate-sensing leads using an Intermedics pacing system analyzer model 524-01 before implantation of the AICD. The R wave was 10 mV in the first dog, 12 mV in the second, and 15 mV in the third.

After implantation of the device, electrocautery was applied to the edge of the thoracotomy incision using a Valley Lab electrocautery, model SSE3B, in both the unipolar cut and unipolar coagulation modes with maximum output of 112 W and 255 W, respectively. The QRS synchronous tones were monitored for any change in frequency, and an AICD-check probe was held over the AICD to detect charging should it occur.

In no instance was any change in the frequency of the auditory QRS synchronous tones detected, nor did charging of any device occur. In 1 dog, repeated rapid on/off sequences were performed to see if this could cause sensing of the electrocautery. It did not. With the rate-sensing leads disconnected from the dog's heart, the electrocautery was easily detected by the device as noted by the emission of beeps. We were also able to cause AICD sensing of electrocautery by breaking contact between the grounding plate and the animal.

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Clinical Use

Based on this preliminary animal work, 3 of our patients (2 with a model 1550 and 1 with a model 1520) underwent five surgical procedures in which electrocautery was used with the device left on. The devices were monitored with the AICD-check over the device and a magnet in place to detect ARS synchronous tones so that we could monitor for sensing of the electrocautery.

One patient underwent revascularization of the right lower extremity using a vein graft. Several months later, he had an above-the-knee amputation after the vein graft failed. During both procedures, unipolar electrocautery was performed using an Aspen Labs model MF 380 with an output of 39 W in the coagulation mode and 36 W in the cut mode. The second patient had a penile prosthesis inserted. The same electrocautery device was used with a coagulation mode output of 30 W and a cut mode output of 31 W. The third patient underwent endoscopic bipolar electrocautery in the stomach for gastrointestinal bleeding using a Circon ACMI BICAP electrocautery source with a setting of 8 and a duration of 2 seconds. In no instance did sensing of electrocautery signals, device charging, or other device malfunction occur.

Comment

We believe that it is not necessary to deactivate the present CPI devices during elective surgical procedures because of concerns about potential interactions with electrocautery. Attention should be paid to proper grounding when unipolar cautery is used, as improper grounding may permit the device to sense signals generated by electrocautery.

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Long-Term Results After Atrial Correction of Complete Transposition of the Great Arteries

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This study presents the late results for the first 104 consecutive patients surviving an atrial repair for transposition of the great arteries (TGA) between January 1971 and December 1978 (group 1). Mean follow-up was 12 years (range, 0.1 to 17.7 years). The actuarial survival rate at 18 years was 84.2% (70% confidence limits, 79% to 88%) for simple TGA and 93.7% (70% confidence limits, 84% to 97%) for complex TGA. Nine of the 11 deaths were sudden. Two (2.6%) of the 78 late survivors operated on for simple TGA are in New York Heart Association functional class III or IV versus 4 (26.7%) of the 15 survivors with complex TGA; the other patients are doing very well. To better assess long-term results, we report the findings for randomly obtained electrocardiograms, Holter monitor recordings, radionuclide angiographic studies, and cardiac catheterizations performed in 1987 in a larger group of 159 long-term survivors of atrial repair operated on at Ospedale Riuniti di Bergamo from January 1971 to December 1984 (group 2), which includes all of group 1. The findings confirm that the arterial switch repair is the procedure of choice for complex TGA and that there is a major incidence (approximately 10%) of systemic right ventricular dysfunction and rhythm disturbances after the atrial repair. On the other hand, our late survival rate at 18 years of 84% for simple TGA with 97.5% of the patients in functional class I is a result that should be kept in mind, especially in institutions where the arterial switch is a relatively new approach and presumably is a higher risk to cause early death.

(Ann Thorac Surg 1991;51:227–31)

Transposition of the great arteries (TGA) accounts for 5% to 7% of all cardiac malformations [1, 2]. Its very high mortality rate (about 90% during the first year of life without treatment [3]) has resulted in a continual search for adequate methods of treatment since the early years of cardiac surgery. Currently two types of definitive treatment are available: the so-called atrial repair or physiological correction and the anatomical correction. The atrial repair includes the Mustard [4] and Senning [5] operations and is based on a rerouting of the systemic venous return through the mitral valve and of the pulmonary venous return through the tricuspid valve. Though ingenious, this type of repair involves extensive atrial procedures, which can lead to atrial arrhythmias and obstruction of the venous pathways, and requires the anatomical right ventricle to sustain the systemic circulation for life with the potential for late ventricular dysfunction. The anatomical repair includes the arterial switch, the Rastelli operation, and their numerous modifications. All these operations have technical drawbacks that have prevented good short- and long-term results until recently.

A progressive reduction in perioperative mortality and encouraging intermediate-term results after the arterial switch operation in neonates in some institutions [6–8], together with the theoretical advantages of an anatomical repair, represent powerful arguments in favor of this newer procedure for all cardiac surgical centers. As a consequence, before engaging in the routine performance of the arterial switch operation in neonates, we undertook a long-term follow-up study of patients who underwent atrial repair at Ospedale Riuniti di Bergamo.

Material and Methods

This study includes the first 104 consecutive patients surviving an atrial repair (Senning or Mustard) for TGA at our institution between January 1971 and December 1978 (group 1). Eighty-eight patients had simple TGA, and the other 16 had a complex form (ventricular septal defect [VSD] larger than 3 mm, pulmonary stenosis, or both). Age at operation ranged from 0.04 year to 10 years with a mean of 1.4 years, and weight at operation ranged from 2.8 to 26 kg with a mean of 7.5 kg. A Mustard procedure was performed in 87 patients and a Senning repair, in 17.

All patients have been seen periodically in the outpatient clinic of our institution, and the condition of each has been evaluated by clinical examination, electrocardiography, and chest roentgenography. During the year 1989, all patients were contacted except 1, whose last examination was October 1987. The clinical status of each patient was reassessed at that time to obtain up-to-date survival and reoperation-free Kaplan-Meier curves. The mean follow-up of our 104 patients was 12 years (range, 0.1 to 17.7 years).

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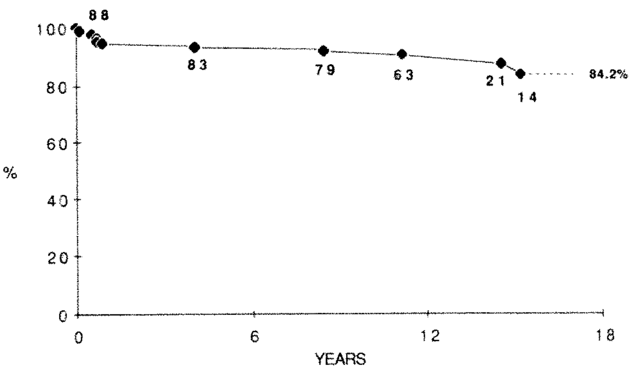

Fig 1. Actuarial survival of patients with simple transposition of the great arteries who underwent atrial repair before 1979.

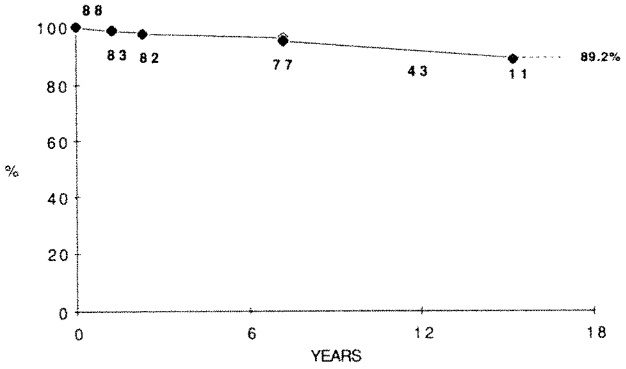

Fig 3. Reoperation-free survival of patients with simple transposition of the great arteries who underwent atrial repair before 1979.

To better assess long-term results other than clinical status, we also report the findings of a series of investigations performed during 1987 in a larger group of 159 long-term consecutive survivors of atrial repair for TGA operated on at our institution from January 1971 to December 1984 (group 2); all group 1 patients are included. Rhythm disturbances, residual anatomical defects, and ventricular function were evaluated. Specifically, electrocardiographic studies (110 patients), two-dimensional echocardiographic studies (40 patients), Holter monitor recordings (33 patients), radionuclide angiocardiographic studies (13 patients), and cardiac catheterization (18 patients) were performed. Patients were selected at random. The average follow-up was 7.2 years.

Results

Group 1

The overall late mortality rate in the study group (follow-up longer than 10 years) is 10.57% (11/104 patients). Ten (11.4%; 70% confidence limits [CL], 7.8% to 16%) of the 88 patients with simple TGA and 1 patient (6.3%; 70% CL, 0.8% to 19.7%) of the 16 with complex TGA died. The actuarial survival curves for simple (Fig 1) and complex (Fig 2) TGA show that 84.2% (70% CL, 79% to 88%) and 93.7% (70% CL, 84% to 97%), respectively, of the patients are expected to be alive 18 years after the operation; after 12 years of follow-up, there are 48 patients with simple and 12 patients with complex TGA under observation. The differences in mortality rate and actuarial survival between the patients with simple TGA and those with complex TGA are not significant.

Nine of the 11 late deaths were sudden and occurred at home, and no postmortem examination was done. The overall incidence of sudden death is 9%. Five of the 9 patients showed sinus rhythm on the standard electrocardiogram obtained during their most recent outpatient examination; the remaining 4 showed junctional rhythm or paroxysmal supraventricular tachycardia. One patient died of progressive heart failure 6 months after a Mustard procedure for simple TGA. The other patient died during reoperation (performed elsewhere) for left ventricular outflow tract obstruction that had progressed over the years.

Six patients (5.8%), all treated by a Mustard procedure, required a total of eight reoperations. The actuarial reoperation-free curves for simple and complex TGA are shown in Figures 3 and 4; the differences are not significant, 89.2% (70% CL, 81.8% to 93.8%) for simple TGA and 91.6% (70% CL, 79.4% to 97%) for complex TGA at 18 years.

Two reoperations for pulmonary venous obstruction

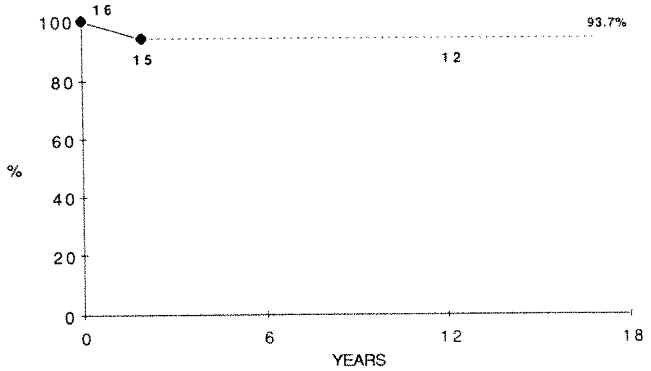

Fig 2. Actuarial survival of patients with complex transposition of the great arteries who underwent atrial repair before 1979.

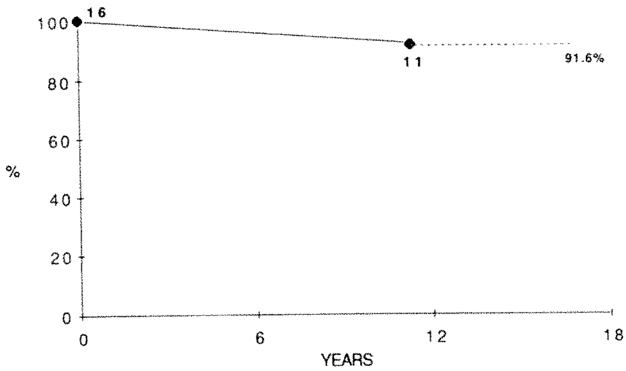

Fig 4. Reoperation-free survival of patients with complex transposition of the great arteries who underwent atrial repair before 1979.

Table 1. Results of Standard Electrocardiograms From 110 Patients

Rhythm	No. of Patients
Sinus, without any associated arrhythmias	88 (80%)
Atrial flutter	1
Pacemaker	2
Junctional, intermittent	7
SVEB	11
VEB Lown I	1

SVEB = supraventricular extrasystolic beat; VEB = ventricular extrasystolic beat.

(the second for obstruction of the inferior vena cava as well) were performed in the patient with the longest follow-up in this study 2.3 years and 7.6 years after the original operation. He is now in New York Heart Association (NYHA) functional class III. One other patient had reoperation for pulmonary venous obstruction 1.2 years after the initial procedure, and 2 patients underwent reoperation for superior vena cava obstruction (7.1 years and 7.2 years after repair). All 3 are in NYHA functional class I.

One patient, already mentioned, died during a reoperation for left ventricular outflow tract obstruction 15.1 years after correction. The last patient had originally undergone a Mustard repair and VSD closure. A moderate left ventricular outflow tract obstruction had been left untouched at that operation; 11.5 years later, he underwent a Mustard takedown and a Rastelli procedure because of a residual VSD and major pulmonary stenosis with a severely impaired right ventricle. A second reoperation for a residual VSD and obstruction of the right ventricle–pulmonary artery conduit was required 1.5 years later. This patient is now in NYHA functional class III. Two additional patients underwent successful balloon dilation of the superior vena cava for asymptomatic obstruction of that vena cava.

Two (2.6%; 70% CL, 1% to 6%) of 78 patients operated on for simple TGA are in NYHA class III or IV at the latest follow-up (1989). Conversely, 4 (26.7%; 70% CL, 14% to 43%) of 15 patients operated on for complex TGA are in functional class III or IV. The other patients are doing very well (NYHA class I), although 3 of them required implantation of a permanent cardiac pacemaker.

Group 2

Standard electrocardiographic recordings in 110 patients showed sinus rhythm in 80% (Table 1), whereas the Holter examination, performed in 33 patients, demonstrated a stable sinus rhythm without associated arrhythmias in only 48.5% (Table 2). Excluding the so-called normal arrhythmias, as detected in the normal population by Holter monitoring [9], the proportion of patients free from pathological rhythm disturbances in this group reaches 69.7%.

Forty patients underwent two-dimensional Doppler echocardiography; all but 2 were asymptomatic. Right ventricular dysfunction (severely hypokinetic systemic ventricles) associated with tricuspid incompetence was demonstrated in 3 patients (7.5%), 2 of whom were patients in poor clinical condition (NYHA class III or IV). Trivial tricuspid insufficiency was shown in 4 patients (10%), major caval obstruction in 3 (7.5%), and pulmonary venous obstruction in 1 patient (2.5%), who subsequently underwent successful reoperation. A left ventricular outflow tract obstruction (mild to moderate) was demonstrated in 5 patients (12.5%); it was fixed in 2 and dynamic in 3. A residual VSD, previously suspected, was confirmed in 1 patient (2.5%), who subsequently had a successful reoperation. Finally, a mild shunt at the atrial level was detected in 1 patient (2.5%).

Radionuclide angiocardiography was performed in 13 asymptomatic patients operated on for simple TGA to assess right and left ventricular function at rest and during exercise. In these patients, follow-up ranged from 6 to 15 years (mean follow-up, 10.2 years). We considered as normal a right ventricular ejection fraction (RVEF) greater than 0.45 and a left ventricular EF greater than 0.50. A normal response to stress was considered an increase in the EF of 0.05 or more [10, 11]. One patient showed a severely abnormal RVEF at rest, and 2 had a slightly decreased RVEF. Five patients had a markedly decreased RVEF under stress. Only 2 patients showed a normal increase in the RVEF under stress. Conversely, only 1 patient had a mildly decreased left ventricular EF at rest but responded normally to stress, and 2 patients demonstrated an abnormal response under stress (they also had an RVEF abnormally responsive to stress, thus indicating global impairment of myocardial function). No correlation was found between the distribution of the RVEFs and left ventricular EFs and either age at operation or length of follow-up.

Hemodynamic studies were performed in 18 randomly

Table 2. Results of Holter Monitoring in 33 Randomly Chosen Patients

Rhythm	No. of Patients
Sinus, without any associated arrhythmias	16[a] (48.5)
Sick sinus syndrome	1
Junctional, intermittent	3
Junctional, intermittent + SVEB	1
Junctional, intermittent + VEB Lown I	1
Junctional, sustained	2
SVEB	3
SVEB + VEB Lown I	4
SVEB + PSVT	1
VEB Lown II	1

[a] In 23 patients (69.7%), no arrhythmias or so-called normal arrhythmias were found.

PSVT = paroxysmal supraventricular tachycardia; SVEB = supraventricular extrasystolic beat; VEB = ventricular extrasystolic beat.

chosen asymptomatic patients at a mean follow-up of 8.2 years after informed consent had been obtained from the parents. Superior vena cava obstruction (gradient = 8 mm Hg) was found in 1 patient, bicaval obstruction in 2 patients (superior vena cava gradients = 8 mm Hg and 11 mm Hg, and inferior vena cava gradient = 5 mm Hg and 4 mm Hg, respectively). Tricuspid insufficiency was found in 4 patients; it was mild in 3 and moderate in 1. Fixed left ventricular outflow tract obstruction (gradient = 50 mm Hg) was detected in 1 patient. Finally, the RVEF was 0.44 and 0.45 in 2 patients, 1 of whom also had mild tricuspid incompetence. Again, no correlation was found between the distribution of RVEFs and the length of follow-up.

Comment

No treatment of a congenital heart disease has varied over the years more than that of TGA. One cannot ignore the impact of the different palliative procedures or that of the partial repair of Baffes [12] in the development of our current concepts. The controversy between the supporters of the Mustard procedure and the supporters of the Senning procedure is recent history.

Waves of enthusiasm and disappointment have been common after the introduction of each new procedure, and the arterial switch repair is no exception. In the recent literature, most reports on the arterial switch are enthusiastic. Emphasis is placed on the low mortality obtainable with this procedure, on the low incidence of postoperative arrhythmias, and on the apparently normal systemic ventricular function. On the other hand, little importance is attributed to the lack of long-term follow-up studies and to the occurrence of complications related to the repair (ie, aortic insufficiency, pulmonary stenosis, or coronary stenoses).

At the same time, a number of studies from several prestigious institutions have reported long-term results of physiological corrections. These studies involving large series of patients have a tendency to emphasize late complications and to forget that 80% to 85% of the operative survivors are alive up to 20 years after the original repair and that 90% of them live a normal life [13, 14]. Our results are meaningful because of the large number of patients followed up for almost two decades. They are comparable with the results reported by Turina and colleagues [13], Williams and associates [14], and Kirklin and Barratt-Boyes [15]. Our late survival rate of 84% at 18 years for simple TGA should be considered, keeping in mind the 96%, 91%, and 90% total survival rate at 1 week, 1 year, and 2.5 years, respectively, reported in the 20-institution study of the arterial switch operation for the so-called low-risk institutions [6].

Moreover, our late mortality pertains to patients operated on in an era in which the atrial repair had the same technical drawbacks as the arterial switch does now, and therefore it can reasonably be assumed that some of our late deaths would not occur today. Specifically, modifications of the surgical techniques of the Mustard procedure have decreased the incidence of pulmonary and systemic venous obstruction, which frequently leads to late death or reoperation. A satisfactory clinical status is the rule among our patients having operation for simple transposition, whereas more than a quarter of those operated on for complex TGA are in NYHA functional class III or IV. This is probably a reflection of several factors, including older age at the time of repair with long-standing hypoxemia and worse ventricular function because of it, and the pressure or volume overload or both in the latter group of patients.

Neonatal age at the time of repair is a strong argument in favor of the arterial switch procedure for simple TGA, but a recent study [16] has shown the feasibility of atrial correction in the neonatal period; the mortality was very low and the medium-term results were excellent. This method may prevent preoperative deaths and probably will ensure even better long-term results.

Right ventricular dysfunction is regarded as a frequent and unfavorable occurrence after physiological correction of TGA. In our simple TGA group, 2 patients (2.6%) have symptomatic evidence of right ventricular failure, and the incidence of right ventricular dysfunction approaches 10% by echocardiographic and catheterization studies. Radionuclide angiographic studies showed only one severely impaired right ventricle at rest, although they did confirm an abnormal response to stress in most patients in our series. Though disturbing, this finding has controversial value, as it applies to abnormally pressure-loaded right ventricles, the normal responses of which are unknown. In a recent report [17], right ventricular function was studied in 8 patients with corrected TGA and no associated anomalies, and functional patterns similar to those observed in atrial switch patients were found. Specifically, in both groups, adequate cardiac indices were obtained with an increase in the heart rate alone rather than the heart rate and the EF. On the other hand, patients with a fixed heart rate (pacemaker dependent) compensated by a marked increase in the EF. All these findings suggest compensatory mechanisms different from the usual ones in response to stress or exercise in these hearts. In this regard, another important result of our study and other studies [17] is the lack of correlation between abnormal right ventricular function and both age at operation and length of follow-up. Finally, the literature contains conflicting data regarding the life expectancy after corrected TGA without associated cardiac anomalies [18, 19].

In summary, our experience shows that right ventricular failure occurs in a small but significant number of patients and that it is unrelated to age and length of follow-up. Abnormal responses to exercise may indicate different compensatory mechanisms and might have little to do with the appearance of subsequent right ventricular failure.

Pulmonary and systemic venous obstructions necessitating reoperation or balloon dilation have been found in 6% of our patients, and all have been successfully treated. An accepted opinion [20] is that the occurrence of pulmonary venous obstruction should become extremely rare with proper techniques (ie, V-Y procedure) and systemic venous obstruction can often be treated with balloon angioplasty.

Postoperative arrhythmias have been noted since the early days of atrial repair of TGA, and modifications of the surgical techniques have been developed in unsuccessful efforts to decrease the incidence and severity of these arrhythmias. Reports of long-term results have shown a progressive decline in sinus rhythm at a constant rate in survivors of Mustard and Senning repairs. The 30% of patients with pathological arrhythmias at a mean follow-up of 7.2 years in our study is not significantly different from the data reported in the recent literature [14, 21]. According to recent data [14], 53% of patients, at the most, can be expected to be free from junctional rhythm 20 years after the Mustard operation. These data and the substantial number of unexplained sudden deaths are powerful arguments against the physiological repair.

The arterial switch repair, however, involves reimplantation of the coronary arteries, and complete occlusion of the left anterior descending coronary artery has been reported after this type of operation [22]. Even though this finding is not necessarily associated with myocardial infarction or with persistent myocardial ischemia, sudden deaths, myocardial infarctions, perfusion defects, and arrhythmias have been described [23–25]. Moreover, transient ischemic alterations are frequent early after the arterial switch repair. These observations raise some concerns about the future occurrence of left ventricular deterioration and arrhythmias in the late follow-up of these patients.

The data from this series confirm the arterial switch repair to be the procedure of choice for TGA with VSD. Maybe this will be the case for simple TGA; also this notwithstanding, an excessive enthusiasm for the arterial repair for simple TGA should be a matter of concern. We are referring especially to those institutions where this surgical option is a relatively new approach and is presumably at higher risk to cause early death. A recent report [16] on atrial repair for simple TGA showed no early deaths and a late survival rate of 97% with a mean follow-up of 10 years. Its results should be taken into consideration when determining the better approach to this malformation.

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Pulmonary Embolectomy: A 20-Year Experience at One Center

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Between 1968 and 1988, 96 consecutive patients with acute massive pulmonary embolism underwent pulmonary embolectomy under cardiopulmonary bypass. The operative mortality rate was 37.5%. We analyzed 12 clinical and hemodynamic variables by univariate and multivariate analyses to assess the predictive factors of postoperative outcome. Multivariate analysis disclosed that cardiac arrest and associated cardiopulmonary disease were independent predictors of operative death. Long-term follow-up (range, 2 to 144 months; mean, 56 months) information was available for 55 of the 60 discharged patients: 6 had died, and 5 complained of persistent mild or severe exertional dyspnea (New York Heart Association class II). These results help assess the preoperative risk in patients undergoing pulmonary embolectomy. They also show that, in the few patients who do not benefit from optimal medical therapy, pulmonary embolectomy remains an acceptable procedure in view of the long-term results.

(Ann Thorac Surg 1991;51:232–6)

Massive pulmonary embolism (PE) remains an important cause of death despite recent advances in medical therapy. Currently, thrombolysis is widely accepted as the front-line treatment for most patients with massive PE. It is, however, contraindicated in a variety of situations often associated with this disease [1]. Moreover, treatment failure is observed in 15% to 20% of patients [2] and can lead to death in the most severe cases [3, 4]. Although it is estimated that 2% to 6% of patients would benefit from pulmonary embolectomy [5], currently available information on factors associated with operative death and long-term outcome is scant. In an effort to gain a broader understanding of predictive factors of postoperative outcome, we have analyzed our experience with pulmonary embolectomy under cardiopulmonary bypass (CPB) in 96 patients.

For editorial comment, see page 179.

Material and Methods

Patient Population

Over the past 20 years, pulmonary embolectomy under CPB was performed in 96 patients with massive PE. There were 50 men and 46 women ranging in age from 19 to 77 years (average age, 52 years). A causative factor for PE was found in 67 patients (70%): general surgical procedure in 28, gynecological procedure in 5, multiple injuries and orthopedic procedure in 23, and medical disease in 11. A preexisting cardiopulmonary disease was present in 11 patients (11%) and included resected bronchial carcinoma in 2, chronic obstructive pulmonary disease in 3, chronic heart failure in 3, and previous myocardial infarction in 3. Sixty-seven patients (70%) had had one or more preoperative recurrent episodes of PE. The interval between the first episode and pulmonary embolectomy ranged from 1 day to 219 days and averaged 14 days.

On initial examination, systolic blood pressure was 100 ± 26 mm Hg; heart rate, 124 ± 20 beats per minute; and respiratory rate, 31 ± 7 cycles per minute (mean ± standard deviation). On admission, 78 patients (81%) had sustained acute shock, ie, diffuse cutaneous vasoconstriction and peripheral cyanosis despite inotropic support. Cardiac arrest necessitating closed chest massage occurred in 24 patients (25%) before the operation.

Preoperative Investigations

Eighty-five patients underwent right heart hemodynamic evaluation before operation (Table 1). Selective bilateral pulmonary angiography was performed in 92 patients and scored according to the method of Miller and colleagues [6]. The preoperative angiographic score was 28 ± 2.3 (percent vascular obstruction, 82% ± 7%). Four patients were so critically ill that embolectomy was undertaken immediately on the basis of a highly suggestive perfusion lung scan. Of the 73 patients who had inferior venacavography, 7 (10%) had caval thrombosis.

Indications for Embolectomy

The indications for pulmonary embolectomy were as follows: severe hemodynamic impairment precluding any attempt at medical therapy in 43 patients (45%), massive angiographic obstruction in 13 (14%), early failure of thrombolytic treatment in 30 (31%), and contraindication to thrombolytic therapy in 10 (10%).

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Table 1. Preoperative Hemodynamic and Blood Gas Values

Variable	No. of Patients	Value[a]
PaO_2 (mm Hg)	81	51 ± 12
$PaCO_2$ (mm Hg)	81	31 ± 5
pH	81	7.46 ± 0.06
RAP (mm Hg)	85	10 ± 5
PAP (mm Hg)	82	32 ± 7
CI ($L/min/m^2$)	79	2.0 ± 0.8
TPRI (U/m^2)	79	18.4 ± 7.8

[a] Values are shown as the mean ± the standard deviation.

CI = cardiac index; $PaCO_2$ = partial pressure of arterial carbon dioxide; PaO_2 = partial pressure of arterial oxygen; PAP = mean pulmonary artery pressure; RAP = right atrial pressure; TPRI = total pulmonary resistance index (mean PAP/CI).

Surgical Technique

All patients were operated on using total CPB under normothermia and without aortic cross-clamping. In 17 patients, partial bypass through the femoral vessels was instituted in the operating room before initiation of total CPB. Median sternotomy and cannulation of the venae cavae and ascending aorta were rapidly performed. Clots were removed through a longitudinal incision in the main pulmonary artery by manual extraction and use of common bile duct forceps. A standard sucker was used to extract the most distal clots. In 24 patients, the pleura was opened and both lungs were massaged to express peripheral clots. The right atrium and ventricle were explored, and the vena cava was flushed for residual clots.

Ligation or clipping of the inferior vena cava was performed in 38 patients. In 38 other patients, an intravenous filter was inserted postoperatively an average of 3 days after operation (range, 1 to 12 days). Vena caval interruption was not undertaken in 20 patients because of early death (15 patients) or for technical reasons (5 patients).

Follow-Up

A formal follow-up of all patients not known to be dead was carried out through hospital outpatient visits or by telephone interviews with the patient, the patient's physician, or both. Among the 60 patients discharged from the hospital, follow-up information was obtained from all but 5. The mean follow-up was 56 months (range, 2 to 144 months).

Statistical Analysis

All data were analyzed by means of the BMDP statistical software package (BMDP Statistical Software, Los Angeles, CA). Univariate analysis of factors that might affect hospital mortality was performed by χ^2 test or Fisher's exact test as appropriate. Multivariate analysis was performed by stepwise logistic regression [7]. The following preoperative clinical variables were analyzed: sex, age, associated cardiopulmonary disease, shock, cardiac arrest, date of pulmonary embolectomy, delay between the first clinical episode of PE and the operation (≤15 days), and preoperative thrombolytic therapy. In the subgroup of patients who underwent a complete hemodynamic assessment, mean pulmonary artery pressure and cardiac index were also tested. The effects of select variables were expressed by odd ratios (and 70% confidence limits), which approximate the relative risk, ie, the incidence rate for an exposure category divided by the corresponding rate in the comparison group [7]. These ratios were adjusted for other factors retained in the final model. The interaction among variables and the validity of the logistic model for the present data were also assessed [8]. A paired *t* test was used to assess the significance of differences between the preoperative and the postoperative hemodynamic variables.

Results

Early Results

Massive PE was consistently confirmed at the time of surgical exploration. In 9 patients, major clots were found in the right atrium. A pericardial hemorrhagic effusion, probably caused by a perforation of the right ventricle during angiography, was discovered in 3 patients.

The overall hospital mortality rate was 37.5%. Table 2 shows the causes of the 36 operative deaths. Eight patients died of early massive pulmonary hemorrhage. The mechanism of this dramatic complication remains unclear, and no obvious preoperative predictor was identified. Of the 60 hospital survivors, 28 (47%) experienced perioperative complications. Adult respiratory distress syndrome occurred in 11 patients and bleeding, in 8. Eight patients had infectious complications, two of which were mediastinitis. Other complications were neurological damage in 5 patients, acute renal failure in 5, and heparin sodium-induced thrombocytopenia in 5.

Right heart catheterization and pulmonary angiography were performed 10 ± 7 days postoperatively on 59 patients. The mean pulmonary artery pressure decreased

Table 2. Causes of Operative Death

Cause	Total	Intraoperative
Cardiogenic shock[a]	13	6
Pulmonary hemorrhage	8	6
Mediastinitis	4	0
Other infection	3	0
Neurological damage	2	0
Bleeding	1	0
Recurrent pulmonary embolism	1	0
ARDS	2	0
Unknown	2	0
Total	36	12

[a] This includes right ventricular failure (4 patients), left ventricular failure (6 patients), and cardiogenic shock of unknown etiology (3 patients).

ARDS = adult respiratory distress syndrome.

Table 3. Univariate Analysis of Risk Factors for Death: Clinical Variables in 96 Patients[a]

Variable	No. of Patients (n = 96)	Nonsurvivors (n = 36)	Survivors (n = 60)	p Value
Sex				
Male	50 (52)	23 (46)	27 (54)	0.073
Female	46 (48)	13 (28)	33 (72)	
Date of operation				
1968–1978	19 (20)	6 (32)	13 (68)	0.42
1979–1983	45 (47)	20 (44)	25 (56)	
1984–1988	32 (33)	10 (31)	22 (69)	
Associated heart or lung disease				
Yes	11 (11)	7 (64)	4 (36)	0.061
No	85 (89)	29 (34)	56 (66)	
First clinical episode				
>15 days	21 (22)	9 (43)	12 (57)	0.57
≤15 days	75 (78)	27 (36)	48 (64)	
Shock				
Yes	78 (81)	33 (42)	45 (58)	0.043
No	18 (19)	3 (17)	15 (83)	
Cardiac arrest				
Yes	24 (25)	14 (58)	10 (42)	0.015
No	72 (75)	22 (31)	50 (69)	
Thrombolysis				
Yes	30 (31)	7 (23)	23 (77)	0.053
No	66 (69)	29 (44)	37 (56)	
Age (y)[b]	52 ± 14	55 ± 12	50 ± 15	0.055

[a] Numbers in parentheses are percentages. [b] Data are shown as the mean ± the standard deviation.

Table 4. Univariate Analysis of Risk Factors for Death: Angiographic and Hemodynamic Data[a]

Variable	No. of Patients	Survivors	Nonsurvivors	p Value
PAP (mm Hg)	82	32 ± 8	33 ± 8	0.44
CI (L/min/m^2)	79	2.1 ± 0.8	1.8 ± 0.5	0.062
TPRI (U/m^2)	79	17.1 ± 6.5	20.6 ± 9.2	0.056
PVO (%)	92	81 ± 7	84 ± 6	0.11

[a] Data are shown as the mean ± the standard deviation.

CI = cardiac index; PAP = mean pulmonary artery pressure; PVO = percent vascular obstruction; TPRI = total pulmonary resistance index.

from 33 ± 8 mm Hg preoperatively to 16 ± 5 mm Hg postoperatively ($n = 30$; $p < 0.001$), and the cardiac index increased from 2.0 ± 0.9 L/min/m^2 to 3.0 ± 0.6 L/min/m^2 ($n = 28$; $p < 0.001$). The Miller index decreased from a preoperative level of 28 ± 2 to 10 ± 5 at the time of the postoperative examination ($n = 57$; $p < 0.001$).

Risk Factors for Death

Among the clinical variables tested by univariate analysis in the 96 patients, only preoperative cardiac arrest and shock were different at the 5% level between survivors and nonsurvivors (Table 3). The operative mortality rate of patients with and without preoperative cardiac arrest was 58% (14/24) and 31% (22/72), respectively. Similarly, it was 42% (33/78) for patients with preoperative shock compared with 17% (3/18) for those without shock. In the subgroup of 79 patients who underwent a complete hemodynamic assessment, the univariate analysis did not reveal any predictor of postoperative death, although cardiac index and total pulmonary resistance index were of borderline significance (Table 4).

In the entire group of patients, multivariate analysis subsequently identified cardiac arrest and associated cardiopulmonary disease as two variables predictive of operative death and increasing the mortality risk by 3.4 and 4.7, respectively (Table 5). In the previously defined subgroup of 79 patients, multivariate analysis also showed cardiac arrest and associated cardiopulmonary disease to be independent predictors of postoperative death (Table 6).

Long-Term Results

Six patients died 2 to 90 months after operation as a result of cancer (3 patients), multiple injuries (1 patient), aplastic anemia (1 patient), and unknown cause (1 patient). Among the 55 hospital survivors on whom follow-up information was available, 39 (71%) showed no signs of cardiac or pulmonary functional limitation, and 16 (29%) complained of exertional dyspnea. Eleven of these patients were in New York Heart Association functional class I, and 5 were in class II. Among these 16 patients, only 1 had had a preoperative cardiopulmonary disease. The interval between the first embolic event and embolectomy averaged 13 days (range, 1 to 110 days) in the 16 symptomatic patients compared with 10 days (range, 1 to 90 days) in the 39 symptom-free survivors. Ten patients had some degree of leg swelling related to caval interruption. A perfusion lung scan done an average of 13 months

Table 5. Multivariate Analysis (Logistic Regression) of Incremental Risk Factors for Postoperative Death: Clinical Variables in 96 Patients

Incremental Risk Factor[a]	Logistic Coefficient (±SE)	p Value	Increase in Incidence[b]	
			Mean	CL
Cardiac arrest	1.22 ± 0.55	0.025	3.4	1.9–5.9
Associated heart or lung disease	1.55 ± 0.77	0.045	4.7	2.2–9.9
Male sex	0.93 ± 0.50	0.062	2.6	1.6–4.2
Shock	1.19 ± 0.76	0.12	3.3	1.6–6.9
Age	0.03 ± 0.02	0.18	. . .	. . .
Intercept	−3.86 ± 1.25			

[a] Thrombolysis was not retained in the model ($p > 0.20$). [b] This shows the odd ratio and 70% CL.

CL = confidence limits; SE = standard error.

Table 6. Multivariate Analysis (Logistic Regression) of Incremental Risk Factors for Postoperative Death in 79 Patients Who Underwent Complete Hemodynamic Evaluation

Incremental Risk Factor	Logistic Coefficient (±SE)	*p* Value	Increase in Incidence[a] Mean	CL
Cardiac arrest	1.70 ± 0.66	0.013	5.4	2.8–10.6
Associated heart or lung disease	1.62 ± 0.78	0.035	5.0	2.3–10.9
Age	0.05 ± 0.02	0.071	. . .	. . .
Intercept	−3.44 ± 1.33			

[a] This shows the odd ratio and 70% CL.

CL = confidence limits; SE = standard error.

after operation (range, 1 to 74 months) was available for 38 patients. Fourteen of these patients had dyspnea on exertion, and 24 were asymptomatic. The scintigraphic defect in these two groups was 16% ± 19% and 9% ± 13%, respectively ($p = 0.23$).

Comment

During a 20-year period, 96 (3%) of 3,000 patients who were referred to our institution for confirmed PE underwent pulmonary embolectomy under CPB. Our 37.5% mortality rate is close to the 40% quoted by Del Campo [9] for 537 patients who underwent pulmonary embolectomy under CPB from 1965 to 1982, yet reported mortality rates vary from one institution to another within a range of 11% to 55% [10, 11]. Although these differences may be due to the degree of preoperative hemodynamic impairment, current published material remains imprecise about the preoperative status of patients.

To predict more accurately the outcome of patients undergoing pulmonary embolectomy, we analyzed the preoperative factors that could account for postoperative death. Among the 12 clinical and hemodynamic variables that we tested, cardiac arrest and associated cardiopulmonary disease were independent factors predictive of postoperative death. In a series of 71 embolectomies performed under CPB, Gray and co-workers [12] reported a hospital mortality of 11% among patients who had not sustained cardiac arrest before operation and 64% among those who had. In contrast, the role of preexisting cardiopulmonary disease has not previously been emphasized. In our study, age and shock were factors of borderline significance, but they should probably be considered additional indicators of an unfavorable postoperative outcome. Finally, the interval between the first embolic episode and the operation was not a predictor of postoperative death. Therefore, we believe that a clinical history of more than 15 days should not preclude surgical intervention. Similarly, initiation of thrombolytic therapy a few hours before operation did not increase the risk of bleeding or of operative death.

Right heart catheterization was performed on 85 of our 96 patients before pulmonary angiography and confirmed the major right ventricular strain from massive pulmonary embolization. Among the 79 patients who underwent a complete hemodynamic assessment, univariate analysis did not reveal any hemodynamic predictor of postoperative death. In this subgroup of patients, multivariate analysis added no new information or insights. Cardiac arrest and associated cardiopulmonary disease again appeared to be independent indicators of operative death. It is our opinion that, as all patients had severe vascular obstruction, hemodynamic and angiographic abnormalities were of similar magnitude, thus failing to predict postoperative outcome.

During a follow-up of 56 months on average, only six late deaths (11%) occurred among the 55 discharged patients. In 5 of the 6 patients, death did not result from recurrent embolization or postembolic pulmonary hypertension. These observations are in line with previous studies [13, 14] that did not reveal late death from unresolved PE, even among patients who underwent pulmonary embolectomy. This tends to indicate either that the causative factor of PE had disappeared or that recurrent embolization was prevented by vena caval interruption or long-term anticoagulation. The low mortality rate over the long-term follow-up could result in part from the preoperative selection of patients who did not have a terminal disease, especially uncontrolled metastatic malignancies. Like others [14], our results indicate that in patients with a non–life-threatening disease, including those cured of cancer, pulmonary embolectomy is an acceptable procedure in regard to late mortality. In our experience, late mortality was mainly due to an occult malignant disease. This relationship between PE and cancer is already widely accepted [15]. Most long-term survivors had minimal residual obstruction on late perfusion lung scans as well as no clinical symptoms or only mild pulmonary discomfort. This observation is in agreement with previous studies [13, 14, 16] that did not demonstrate any incidence of chronic cor pulmonale after acute PE. Finally, the interval between the first clinical symptoms and pulmonary embolectomy did not differ between symptomatic and asymptomatic long-term survivors and might not be in itself an accurate indicator of the chronicity of the emboli.

The role of pulmonary embolectomy in treating massive PE remains controversial. Some investigators [17] have stated that pulmonary embolectomy was never indicated in massive PE, but others [18] have suggested that surgical intervention should be considered more often, even in patients with no hemodynamic disturbances. We believe that, unless contraindicated, most patients with acute massive PE should be treated with a thrombolytic agent. Pulmonary embolectomy should be considered for hemodynamically compromised patients only if thrombolytic treatment is contraindicated and for those patients so severely affected that the time required for an attempt at medical treatment is thought to be unacceptable. Surgical intervention must also be strongly considered for patients whose condition worsens despite intensive medical treatment. Although there is evidence to suggest that some patients in shock will survive without operation [3, 19], a randomized trial of embolectomy versus medical therapy is unavailable, and it is unlikely that such a trial will ever be performed. Therefore, the decision regarding operation still has to be made on a case-by-case basis. Although our study pinpoints the factors that are associated with an increase in operative mortality, a similarly designed study could help identify factors that can predict death or the need for surgical intervention or both in medically treated patients.

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When Do Cerebral Emboli Appear During Open Heart Operations? A Transcranial Doppler Study

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The transcranial Doppler technique enabled the detection of cerebral air emboli in 10 of 10 patients during open-heart valve operations despite standard deairing procedures. With this technique, the occurrence of emboli in the right middle cerebral artery was followed continuously in patients undergoing aortic or mitral valve replacement. Membrane oxygenators were used. Scattered emboli were observed during the insertion of the aortic cannula, at the start of cardiopulmonary bypass, and after the declamping of the aorta with the heart beating while empty. During the period of aortic cross-clamping, no emboli were detected. Despite careful deairing procedures, the recordings indicated a large amount of emboli during filling of the empty beating heart in all 10 patients. Thus, this study indicates that cerebral emboli in open heart procedures are most likely to occur during the redistribution of blood from the heart-lung machine to the patient when the heart is beginning to eject actively, despite careful standard deairing procedures. Meticulous deairing before declamping the aorta is strongly advocated. In addition, a short period of filling of the beating heart before final closure of the aortic incision or vent may decrease the incidence of cerebral emboli. A concomitant reduction in cerebral blood flow by hyperventilation or anesthetics or both during filling of the empty beating heart may also be beneficial.

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Air embolization to the brain is always a risk in open-heart operations and can destroy an otherwise excellent surgical procedure. The need for air evacuation is accepted in routine valve procedures, but both principles and timing of deairing vary between surgical centers. The traditional view is that the most critical periods for air embolism are immediately after the declamping of the aorta and in conjunction with the cessation of cardiopulmonary bypass (CPB).

The development of ultrasound Doppler techniques, including the transesophageal approach, enables intraoperative imaging of heart function as well as blood flow in heart chambers and through valves. With this method, air embolization from the heart is very frequently observed even after standard deairing procedures [1]. Air emboli to the brain can be detected with the transcranial Doppler technique [2–4]. The transcranial Doppler method allows continuous measurement of blood flow velocity in basal cerebral arteries during cardiac operations [5, 6], and the appearance of emboli creates distinct changes in the flow velocity spectrum [2]. Earlier studies of cerebral emboli during heart operations with the transcranial Doppler technique, however, have been restricted primarily to closed heart operations.

In this study, the appearance of emboli in the middle cerebral artery was monitored continuously with the transcranial Doppler technique during open heart procedures. The aim was to detect and identify periods during which cerebral microemboli occur.

Material and Methods

The study comprised 10 patients undergoing elective aortic or mitral valve replacement. Anesthesia was induced with sodium thiopental and fentanyl and was maintained with fentanyl and isoflurane. Pancuronium bromide was used for muscle relaxation. Nitrous oxide was used only before CPB.

Only flat membrane oxygenators (model M 2000; Shiley Incorporated, Irvine, CA) without arterial filters were used. The crystalloid prime was run for 10 minutes through the circuit and a 5-μm filter before CPB. During CPB, patients were cooled to a nasopharyngeal temperature of 25° to 30°C. A modified St. Thomas' cardioplegic solution (Pharmacia, Uppsala, Sweden) was used. One aortic and one or two venous cannulas were inserted after heparinization; a single two-stage venous cannula was used for aortic valve procedures and two separate caval cannulas were used for mitral valve procedures. The arterial line was carefully deaired before CPB. A vent was inserted through a pursestring stitch positioned at the base of the right superior pulmonary vein. The left atrial pressure was raised before removal of the vent.

The following deairing procedures were routinely undertaken. Their exact timing and performance varied slightly between surgeons.

1. Immediately before completion of aortic or left atrial closure, suction in the left ventricular vent was turned off to allow slow filling of the heart with blood.

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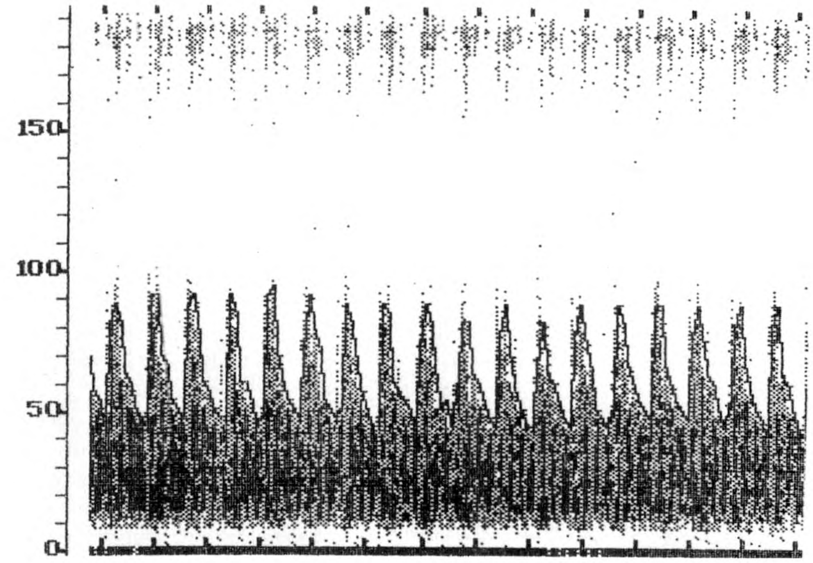

Fig 1. Transcranial sonogram after induction of anesthesia. Time (in seconds) is shown on the abscissa and flow velocity (in cm/s), on the ordinate.

2. The operating table was tilted head down.
3. The lungs were gently inflated to remove any air from the pulmonary veins into the left atrium. Vigorous inflation was avoided.
4. Before the release of the aortic cross-clamp, a large-bore needle was inserted into the aortic root. The aortic or left atrial incision was allowed to bleed freely before definite closure.
5. The heart was squeezed and vigorously vibrated with the hand.
6. The aortic needle vent was not withdrawn until the heart had been ejecting well for about 10 minutes.

Needle aspiration through the left ventricular apex was performed in 2 patients. There was no communication between the investigator and the surgeon regarding the adequacy of the deairing procedures.

A 2-MHz pulsed transcranial Doppler ultrasound velocimeter (model TCD-2-64B; EME, Überlingen, Germany) was used to obtain flow velocity signals from the middle cerebral artery. The ultrasound transducer was placed on the right side of the head just above the zygomatic arch, the thinnest part of the skull. Care was taken to adjust the orientation and depth of the Doppler signals to obtain the best signal strength possible. The position of the probe was fixed in two planes with an EME holder. The holder was then fixed with adhesive tapes to secure a stable position during the operation. The signals were displayed in the form of sonograms (Fig 1). The transcranial Doppler spectrum was analyzed as in previous reports [2–4] in which gaseous and particulate emboli in the bloodstream were well detected by transcranial Doppler ultrasound. The principle for this phenomenon is that emboli larger than the wavelength of ultrasound (approximately 750 μm for 2-MHz ultrasound) reflect rather than scatter sound waves [2]. Thereby, high peaks are added to the ordinary waveform of the velocity spectrum. These clearly audible and visible peaks have been used as a microemboli index [2].

Transcranial Doppler ultrasound allows assessment of the amount of gaseous microemboli passing to the brain, but an adequate quantification of the air volume has proved difficult even with a microcomputer-based system [2, 4, 7]. In this study, findings of emboli were arbitrarily graded 0 through 3 on a microemboli scale (MES): 0 = no air; 1 = 1 to 5 peaks per 8 seconds; 2 = 6 to 10 peaks per 8 seconds; and 3 = more than 10 peaks per 8 seconds or more than 50% up to total shading of the sonogram because of confluent peaks.

The study protocol conformed to the rules of the Helsinki Declaration and was approved by the ethics committee of the University of Uppsala. Informed consent was obtained from patients participating in the study.

Results

Figure 1 shows a representative transcranial Doppler spectrum from the middle cerebral artery after induction of anesthesia. Figure 2 illustrates the flow velocity spectrum in conjunction with nonpulsatile CPB. No embolic events were observed during these two periods (MES = 0).

A transient change in the transcranial Doppler recordings, indicating scattered emboli (MES = 1), was observed in 9 of the 10 patients during insertion of the aortic cannula (Fig 3). With the start of CPB, emboli were observed in 4 of the 10 patients (MES = 1). Immediately after the release of the aortic clamp and in connection with the deairing procedures, small amounts of emboli (MES = 1) were seen. During reperfusion with the heart beating empty, only scattered emboli (MES = 1) were observed.

Figure 4 illustrates a typical transcranial Doppler spectrum during filling of the empty beating heart, leading to ejection of blood into the aorta. In all 10 patients, the recordings indicated a large amount of air bubbles (range, MES = 2 to MES = 3) during this phase. Figure 5 shows the number of embolic events minute per minute in a

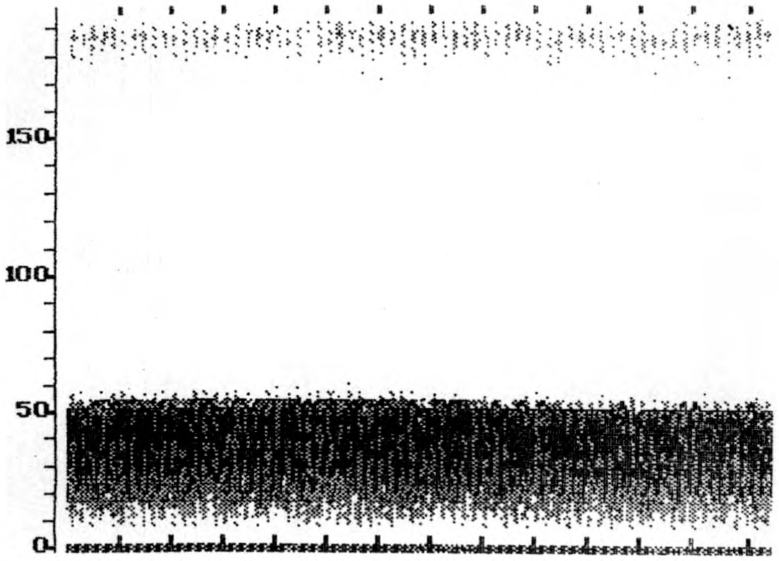

Fig 2. Transcranial sonogram during nonpulsatile cardiopulmonary bypass. See Figure 1 legend for details.

representative patient from before insertion of the aortic cannula to after the end of CPB.

In 2 patients, extensive deairing maneuvers were carefully performed before declamping. They included very vigorous ballottement of the left ventricle and atrium during filling of the heart until no residual air bubbles were seen coming through the aortic needle vent. After defibrillation, during filling of the beating heart and cessation of CPB, only small amounts of emboli (MES = 1 to 2) were seen in these patients.

No neuropsychological testing was performed. At discharge, no neurological sequelae were apparent except in 1 patient in whom simple clinical examination revealed a partial anopsia. Computed tomography confirmed a localized hypodensic zone in the region supplied by the left cerebellar artery.

Comment

The present study indicates that cerebral air emboli in open heart procedures are particularly likely to occur during filling of the beating heart, even after meticulous deairing procedures.

Transcranial Doppler ultrasound enables continuous detection of microemboli passing through basal cerebral arteries [2, 4]. The right middle cerebral artery was studied for two reasons. It supplies 80% of the hemisphere with blood [8], and the right side has a higher probability to receive emboli [9]. Bubble oxygenators were avoided, and only membrane oxygenators, known to be free from continuous microembolization during CPB, were used [2].

No attempts were made to quantify the volume of air passing to the brain. The high resolution of the sono-

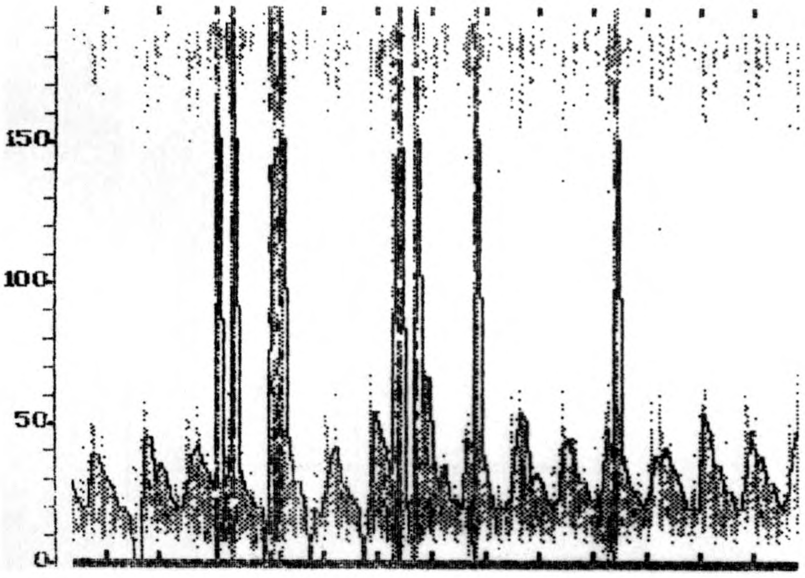

Fig 3. Transcranial sonogram during insertion of the aortic cannula. The peaks indicate scattered cerebral emboli. See Figure 1 legend for details.

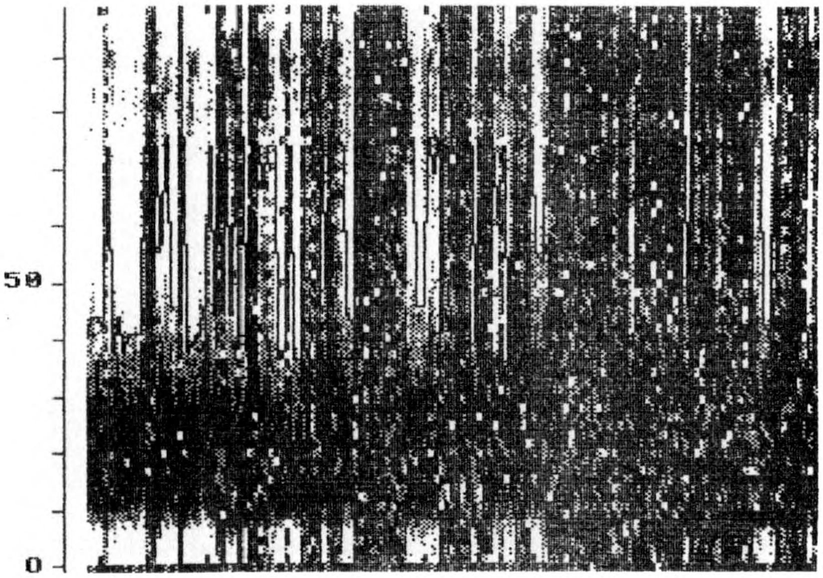

Fig 4. Transcranial sonogram during filling of the empty beating heart. The peaks indicate large amounts of cerebral emboli. See Figure 1 legend for details.

grams, however, enabled us to clearly separate the periods with large amounts of air emboli from those with small amounts or none. The infrequent detection of emboli at the start of CPB indicated adequate deairing of the extracorporeal circuit before CPB. During CPB with the aorta clamped, cerebral emboli were not detected in any patient. In contrast, emboli were most frequently identified in all patients during redistribution of blood from the heart-lung machine to the empty beating heart, when the heart began to eject blood actively.

The cerebral consequences of these findings are open to debate. Obviously, large particulate emboli and massive air embolism will cause more injury than minor embolic events. Particulate emboli can cause stationary obstruction of cerebral vessels, whereas gas emboli have been reported to pass arterioles and capillary beds, leading to the collection of substantial amounts of air in jugular vein traps. Nevertheless, even microbubbles (25 μL) obstructing cerebral arterioles for less than 30 seconds can still disrupt brain function [10]. This may be due to effects that gases have on vascular endothelial cells or blood constituents or both [11–13]. Also, it may explain why many divers who appear to have recovered from cerebral arterial air embolism subsequently have a relapse [14].

Major cerebral injury is easily detected on simple clinical examination, whereas small multiple cerebral injuries caused by microemboli can be hard to document. In this respect, the use of microfilters in the arterial line and

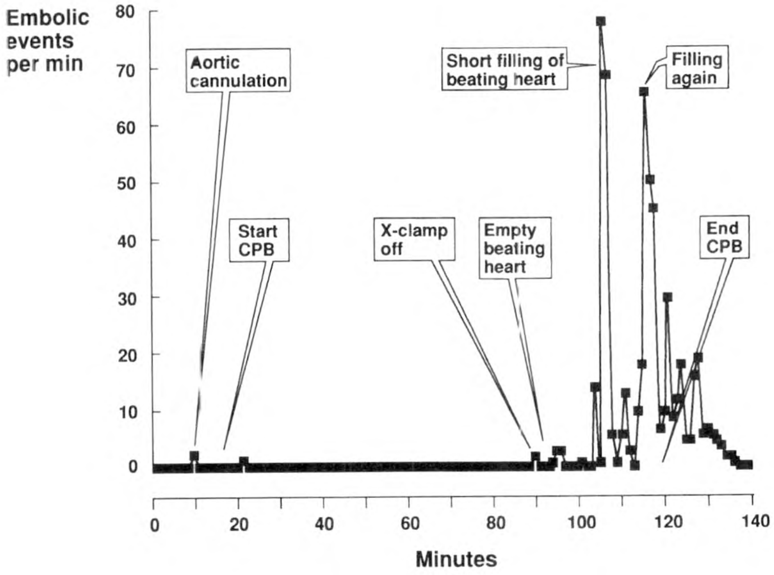

Fig 5. Number of embolic events per minute in a representative patient from before insertion of the aortic cannula to after end of cardiopulmonary bypass (CPB). (X-clamp = cross-clamp.)

cardiotomy return would reduce air and particulate emboli from such sources but would have little impact on embolization directly from the surgical field. In fact, large series [15, 16] confirm the high incidence of severe neurological dysfunction after open heart operations compared with coronary artery bypass grafting. Still, patients undergoing coronary bypass procedures and randomized to arterial filters (40 μm) during bypass with bubble oxygenators have been reported to have fewer detected (transcranial Doppler technique) embolic events and to score better on a verbal memory test 8 weeks after operation than a control group [17].

In this study with flat sheet membrane oxygenators, the microemboli detected in the middle cerebral artery must have come from trapped air and debris in the heart, the pulmonary veins, or the aortic root. Mobilization occurred when the beating heart was filled and began to eject. When deairing was performed with extreme care in 2 patients, it was observed that fewer microemboli passed to the brain. As cerebral emboli were most frequently detected during filling of the beating heart, it may be that the beating heart should be filled before the termination of CPB. This may allow the evacuation of residual air and debris through a still not fully closed aortic incision or aortic vent.

Apart from emphasizing the importance of meticulous deairing before filling of the empty beating heart, the identification of periods likely for cerebral emboli may open up additional approaches to minimize the incidence of both particulate and air emboli to the brain. During these periods, a short elective lowering of the cerebral blood flow, either by a metabolic-depressing anesthetic (ie, thiopental or propofol) or by hyperventilation, may substantially decrease the number of cerebral emboli. The application of bilateral external pressure on the carotid arteries is not recommended because of often-coexisting arteriosclerosis. Controlled studies are needed.

In conclusion, this study indicates that cerebral emboli in open heart procedures are most likely to occur during the redistribution of blood from the heart-lung machine to the patient, when the heart is beginning to eject actively, despite careful standard deairing procedures. Meticulous deairing before declamping the aorta is strongly advocated. In addition, a short filling of the beating heart before final closure of the aortic incision or vent may decrease the incidence of cerebral emboli. A concomitant reduction in cerebral blood flow by hyperventilation or anesthetics during filling of the empty beating heart may also be beneficial.

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Intrathoracic Fibrin Glue for Postoperative Pleuropulmonary Fistula

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Twenty cases of persistent pleuropulmonary fistula after a thoracic surgical procedure were successfully treated with fibrin glue injection into the thoracic cavity through a drainage tube. A new technique, the overlying method, which is a modification of the conventional technique of fibrin glue injection, was devised. Each patient received one to four injections (mean number, 1.6). This method resulted in closure of the pleuropulmonary fistula in all but 1 patient. Minor complications included pain in 1 patient and fever in 3 patients. A control study involving 24 patients with pleuropulmonary fistula was performed. Autoblood, OK-432, and tetracycline were used instead of fibrin glue. The fistula resolved in 12 patients. Complications after injection included pain in 15 patients, fever in 10, and occlusion of the chest tube in 4. With our new method, patients rarely exhibited pain and fever, and occlusion of the chest tube did not occur.

(Ann Thorac Surg 1991;51:242–4)

With the increasing frequency of thoracic surgical procedures in the elderly, postoperative pleuropulmonary fistulas have become major problems. These fistulas are usually closed intraoperatively either by an automatic suturing device or by the application of fibrin glue [1]. However, the fistulas often develop again postoperatively and necessitate further treatment. Generally the treatment consists of the administration of tetracycline, autoblood, or OK-432. These substances, however, cause severe pain, fever, and occlusion of the chest tube. Further, the procedures usually result in insufficient closure of the fistula. Therefore, we devised a new technique of pleural adhesion (overlying method) by modifying the conventional method of fibrin glue injection.

Material and Methods

Between June 1986 and August 1989, 20 patients with a pleuropulmonary fistula were seen at the Second Department of Surgery, Shiga University of Medical Science. There were 17 male and 3 female patients between 17 and 75 years of age (mean age, 60.5 years) (Table 1). Fibrin glue was injected into the thoracic cavity of each patient to treat the pleuropulmonary fistula, which had developed after a thoracic surgical procedure. The duration of the postoperative fistula ranged from 5 to 19 days (mean duration, 10.0 days).

Before injection of fibrin glue, 12 of the 20 patients had been treated as follows: tetracycline injection into the thoracic cavity in 2; OK-432 injection in 2; autoblood injection in 5; embolization of the bronchial tree under bronchoscopic visualization in 2; and closure of the pleuropulmonary fistula with thoracotomy in 1. The remaining 8 patients were treated with fibrin glue injection only.

A control study using other pleural adhesive agents was performed during the same period and comprised 24 patients, 19 men and 5 women between 25 and 77 years of age (mean age, 65.6 years). The injected pleural adhesives were tetracycline in 9 patients, OK-432 in 6, and autoblood in 9. The duration of the postoperative pleuropulmonary fistula ranged from 4 to 12 days (mean duration, 8.9 days).

For the fibrin glue treatment, three kinds of solutions were injected serially through a chest drainage tube (Fig 1): solution A = 1 g of fibrinogen dissolved in 30 to 100 mL of physiological saline solution; solution B = 20 mL of physiological saline solution; and solution C = 70,000 KIU of aprotinin, 10,000 IU of thrombin, 2 mL of 0.5 mol/L $CaCl_2$, and 10 mL of physiological saline solution. The concentration of fibrinogen in solution A was increased according to the grade of the fistula. In the case of fistulas refractory to the first injection, 500 mg of tetracycline was sometimes added to solution C to potentiate the adhesive effect on a higher-grade fistula. In these instances, the tetracycline was dissolved in 20 mL of 2% lidocaine hydrochloride to relieve pain. The solutions were injected through the chest tube in the following order: solution A, solution B, and solution C. Immediately after injection, the tube was clamped, and the patient was rotated. The clamp was released 5 to 10 minutes after injection, and suction of the chest tube was resumed.

In the control study, 500 mg of tetracycline or 5 KE of OK-432 was dissolved in 30 mL of physiological saline solution and 20 mL of 2% lidocaine and then injected. Thirty milliliters of autoblood was injected into the thoracic cavity immediately after the blood was drawn. After injection, the tube, as in the case of fibrin glue injection,

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Table 1. Profile of Patients Injected With Pleural Adhesive Agents

Variable	Fibrin Glue (n = 20)	Other Pleural Adhesives[a] (n = 24)
Age (y)		
Range	17–75	25–77
Mean ± SEM	60.5 ± 13.6	65.6 ± 12.4
Sex		
Male	17	19
Female	3	5
Duration[b] (d)		
Range	5–19	4–12
Mean ± SEM	10.0 ± 3.8	8.9 ± 1.8
Pretreatment		
None	8	24
Tetracycline	2	0
OK-432	2	0
Autoblood	5	0
Bronchoscope[c]	2	0
Thoracotomy	1	0

[a] These agents included tetracycline (9 patients), OK-432 (6), and autoblood (9). [b] This is the duration of the pleuropulmonary fistula after operation. [c] Closure of the fistula was done under bronchoscopic visualization.

SEM = standard error of the mean.

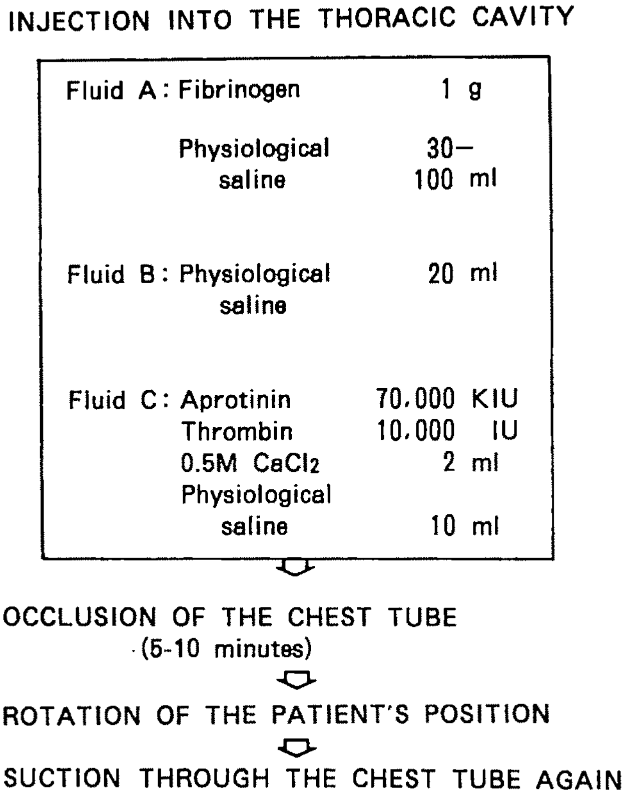
INJECTION INTO THE THORACIC CAVITY
Fluid A: Fibrinogen 1 g
Physiological saline 30–100 ml
Fluid B: Physiological saline 20 ml
Fluid C: Aprotinin 70,000 KIU
Thrombin 10,000 IU
0.5M $CaCl_2$ 2 ml
Physiological saline 10 ml
OCCLUSION OF THE CHEST TUBE
(5-10 minutes)
ROTATION OF THE PATIENT'S POSITION
SUCTION THROUGH THE CHEST TUBE AGAIN

Fig 1. Injection of fibrin glue for chemical pleurodesis.

was clamped, the position of the patient was changed, and suction was resumed.

Results

With the new technique, fibrin glue was injected once in 10 patients, twice in 9 patients, and four times in 1 patient (mean number of injections, 1.6) (Table 2). For 5 patients, tetracycline was added to solution C. Closure of the pleuropulmonary fistula was achieved in all but 1 patient. In that patient, the expansion of the lung was insufficient, leaving a large dead space. Thoracotomy was performed, and the fistula was closed surgically. After the injection of fibrin glue, 1 patient experienced tolerable pain, and 3 patients had fevers lower than 38°C, which returned to normal within a few days (Table 3).

In the control group patients in whom the pleuropulmonary fistula was successfully closed using pleural adhesive agents other than fibrin glue, tetracycline was injected two or three times (mean number of injections, 2.3); OK-432, two or three times (mean number, 2.5); and autoblood, one or two times (mean number, 1.7) (see Table 2). There were 12 patients for whom treatment was unsuccessful; tetracycline was injected in 3 of them, OK-432 in 4, and autoblood in 5. These patients were refractory to two to three injection trials. Among them, 2 who had tetracycline injection, 2 who received OK-432, and 5 who received autoblood were subsequently treated with fibrin glue injection. Of the 24 patients, 15 experienced pain and 10, fever (see Table 3). For 12 of the 15 patients with pain, antipyretic analgesics were administered. Occlusion of the chest tube occurred in 4 patients.

Comment

Pleural adhesive agents are often injected into the thoracic cavity to treat spontaneous pneumothorax and postoperative intractable pleuropulmonary fistula. Many substances, such as tetracycline [2], OK-432 [3], talc [4], and autoblood [5] have been used as pleural adhesive agents. These agents, however, often elicit adverse effects such as severe pain, fever, infection, and occlusion of the chest tube. Jessen and Sharma [6] in 1985 and Glover and colleagues [7] in 1987 reported a new method in which

Table 2. Effect of Pleural Adhesive Agents[a]

		Other Pleural Adhesives		
No. of Injections	Fibrin Glue (n = 20)	Tetracycline (n = 9)	OK-432 (n = 6)	Autoblood (n = 9)
One	10	0	0	3
Two	9	6	3	6
Three	0	3	3	0
Four	1	0	0	0
Mean	1.6	2.3	2.5	1.7
Closure of fistula	19 (95)	6 (67)	2 (33)	4 (44)

[a] Numbers in parentheses are percentages.

Table 3. Complications After Injection of Pleural Adhesive Agents[a]

		Other Pleural Adhesives		
Complication	Fibrin Glue (n = 20)	Tetracycline (n = 9)	OK-432 (n = 6)	Autoblood (n = 9)
Fever	3 (15)	5 (56)	3 (50)	2 (22)
Pain	1 (5)	9 (100)	6 (100)	0 (0)
Occlusion of chest tube	0 (0)	0 (0)	0 (0)	4 (44)

[a] Numbers in parentheses are percentages.

pleuropulmonary fistulas were closed by bronchoscopic injection of a given agent into the bronchus to cause embolization. However, this method often fails to close these fistulas because emboli are frequently dislocated by coughing.

Under these circumstances, fibrin glue injection into the thoracic cavity was used as a non–pain-producing method with a high rate of cure [8]. Nevertheless, a completely satisfactory method to inject fibrin glue has not yet been developed. The usual mixing method allows fibrin glue to react before injection, and the fibrin clot can occlude the chest tube during injection. In addition, the highly concentrated fibrin glue commonly used during the operation is too viscous to diffuse evenly into the thoracic cavity and may fail to cover the pleuropulmonary fistula. Although the concentration of fibrin that we employed is very low, its adhesive effect may be stronger than conventional pleural adhesive agents, judging from clinical observations showing that only a small number of injections were required to produce a high cure rate. Another advantage of our method is that it avoids occlusion of the chest tube by flushing it with physiological saline solution before injection of the reactive solution C.

The fibrin glue overlying method rarely causes the pain and fever common with conventional pleural adhesive agents. In this clinical study, 1 patient treated with the new method experienced both pain and fever. This reaction may have been due to the tetracycline that was mixed with the fibrin glue and injected into the thoracic cavity because of the high grade of the pleuropulmonary fistula. The simplicity of this new procedure as well as its excellent effect on pleuropulmonary fistulas is another major advantage. In addition, the injected fibrin glue is absorbed within 6 months and has no toxic effect on the body [9], a finding that suggests this method is quite safe.

One drawback to our method, which is common to all pleural adhesive agents, is that its effectiveness is limited in lungs that have not expanded sufficiently after injection. Therefore, fibrin glue must be injected after the lungs have been expanded as much as possible either by raising the suction pressure of the chest tube or by bronchoscopic embolization of the bronchus communicating with the pleuropulmonary fistula.

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Retrograde Continuous Warm Blood Cardioplegia: A New Concept in Myocardial Protection

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This report presents the results in our first clinical series of patients receiving continuous warm blood cardioplegia through the coronary sinus. Warm oxygenated blood cardioplegia has certain theoretical advantages, such as continuously supplying oxygen and substrates to the arrested heart while avoiding the side effects of hypothermia. Retrograde infusion of cardioplegia also offers certain advantages (eg, in valve operations and in patients with severe coronary artery disease) that are complementary to warm blood cardioplegia. Retrograde warm blood cardioplegia was used in 113 consecutive patients (85 men and 28 women with a mean age of 61 years) undergoing various procedures. Three percent of the patients died, 7% needed transient intraaortic balloon pump support, 6% had evidence of perioperative myocardial infarction, and 96% had spontaneous return of rhythm. There were no coronary sinus injuries. This new technique of retrograde continuous warm blood cardioplegia is a simple, safe, and reliable method of myocardial protection that may change the way we currently protect the heart intraoperatively.

(Ann Thorac Surg 1991;51:245–7)

Retrograde coronary sinus cardioplegia has been shown to be safe and effective [1–3]. Until recently, its use was somewhat limited because of the difficulties and danger involved in cannulating the coronary sinus for cardioplegia delivery. In 1990, Drinkwater and associates [4] reported the use of a coronary sinus catheter with a self-inflating balloon, which has simplified the technique of coronary sinus cardioplegia. This catheter can usually be inserted into the coronary sinus without the need of direct visualization, and therefore, only rarely will bicaval cannulation and snaring be necessary.

For editorial comment, see page 180.

The purpose of this study is to report the results in our first clinical series of patients undergoing a cardiac operation and receiving continuous warm blood cardioplegia through the coronary sinus with warm body perfusion during cardiopulmonary bypass (CPB).

Material and Methods

Patient Population

Data were obtained from a prospectively collected database as well as a record review of 113 patients who underwent various cardiac procedures using retrograde continuous warm blood cardioplegia and normothermic CPB during a 5-month period. This population consisted of 85 men and 28 women with a mean age of 61 years (range, 21 to 77 years). It is important to note that 25 patients (22%) were more than 70 years old, and 33 (51%) of the patients having myocardial revascularization only were operated on urgently. Furthermore, 44 (39%) of the patients were in New York Heart Association class IV, and 22 (34%) of the patients undergoing myocardial revascularization had had a previous myocardial infarction. Six patients (5%) were operated on urgently for endocarditis. The preoperative diagnoses are listed in Table 1.

Operative Technique

After median sternotomy and heparinization, standard cannulation techniques through the ascending aorta and right atrium were used to complete the CPB circuit. An aortic anterograde cardioplegia cannula (DLP Inc) was placed, and before the initiation of CPB, the retrograde coronary sinus catheter (Research Medical Inc) was positioned using closed transatrial technique. Full CPB was initiated and maintained at normothermia (37°C). While the heart was beating, high-potassium warm blood cardioplegia (resulting from mixing blood 4:1 with high-potassium Fremes' solution*) was infused. The aorta was then clamped.

When the heart was arrested, the cardioplegia line was switched to the fluid-filled retroplegia cannula, and low-potassium warm blood cardioplegia (resulting from a mixture of blood 4:1 with low-potassium Fremes' solution, which has the same ingredients as the high-potassium solution except KCl = 30 mEq/L) was then infused continuously, with the infusion pressure at the

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*High-potassium Fremes' solution comprises the following: 500 mL of 5% dextrose in water; KCl, 50 mEq; $MgSO_4$, 9 mEq; THAM (trihydroxymethylaminomethane), 6 mEq; citrate-phosphate-dextrose solution, 10 mL; osmolality, 425 mosm/L; pH, 7.95.

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Table 1. Preoperative Diagnoses

Diagnosis	No. of Patients
Coronary artery disease	65
Stable angina	32
Unstable angina	28
Failed angioplasty	5
Mitral valve disease	12
Aortic valve disease	28
Mitral valve + coronary artery disease	1
Aortic valve + coronary artery disease	1
Multiple-valve disease	4
Atrial septal defect	1
Cor triatriatum + endocarditis	1

cannula tip maintained at less than 40 mm Hg. The mean flow of cardioplegia in the coronary sinus was 122 mL/min (range, 79 to 234 mL/min). Cardioplegic flow rates varied, and the total administered volume of cardioplegia ranged from 300 to 5,200 mL. The total amount of potassium delivered ranged from 23 to 177 mEq with a mean of 67 mEq. Hyperkalemia was not a clinically significant problem in any patient. The aortic root was vented throughout the cross-clamp period, and retrograde perfusion was assured by noting the engorged oxygenated cardiac veins as well as the return of dark blood through the vent in the aortic root.

Results

The coronary sinus was easily cannulated by the closed transatrial technique in 111 patients (98%). This was not possible in 2 patients (2%), and they required bicaval cannulation and insertion of the retroplegia cannula under direct vision. Placement was facilitated by insertion before the initiation of CPB, and neither major arrhythmias nor hypotension was encountered.

The technique was used in a wide variety of cardiac procedures, as indicated in Table 2. No anomalies of the coronary sinus were encountered. Myocardial revascularization occasionally required intermittent interruption of cardioplegic flow for short periods to perform the anastomoses.

There were three deaths (3%): a 67-year-old woman sustained massive myocardial necrosis secondary to coronary embolization after aortic valve replacement, and 2 male patients who underwent urgent coronary artery bypass grafting died in the intensive care unit in the early postoperative period secondary to graft failures.

Few complications were encountered in this group of patients representing our preliminary experience with this technique. Eight patients (7%) required transient intraaortic balloon pump support for low-output syndrome. Seven patients (6%) had electrocardiographic or cardiac isoenzyme evidence of perioperative myocardial infarction, but there were no subsequent clinical sequelae. Six patients (5%) were returned to the operating room because of bleeding. We observed that 96% of the patients had spontaneous return of rhythm and did not require defibrillation. One patient undergoing aortic valve replacement had heart block and required a pacemaker. There were no coronary sinus injuries.

Comment

Rosenkranz and colleagues suggested that warm induction of cardiac arrest with blood cardioplegia would resuscitate the damaged heart experimentally [5] and clinically [6]. Teoh and associates [7] demonstrated the beneficial effects of terminal warm blood cardioplegia (the so-called hot shot), as suggested by Lazar and co-workers [8]. At the University of Toronto, following Bonfim and co-authors [9], we [10] have used continuous cold (15° to 20°C) oxygenated blood cardioplegia for the last 7 years. Lichtenstein and associates in our group [11] introduced the concept of continuous oxygenated warm blood cardioplegia (warm heart surgery) and recently reported their clinical experience. The advantages of this method are evident when one considers that even short periods of warm blood cardioplegia, either immediately after aortic clamping [6] or immediately before declamping [7, 8], are beneficial to the heart.

Further, it is perhaps time to reassess the effects of hypothermia, introduced clinically by Bigelow and co-workers [12]. It is beyond the scope of this article to review the subject of hypothermia. It is sufficient to note that there are many side effects of hypothermia, such as its effects on membrane stability [13], calcium sequestration [14], glucose utilization [15], adenosine triphosphate generation and utilization [16], tissue oxygen uptake [17], pH [18], cellular osmotic homeostasis [19], and the adenosine triphosphatase system [20], as observed during deep hypothermia.

Table 2. Operative Procedures

Procedure	No. of Patients
CABG	27
CABG with LIMA	36
Redo CABG	2
CABG + mitral valve replacement	1
CABG + aortic valve replacement	1
Mitral valve repair	1
Mitral valve replacement	7
Redo mitral valve replacement	4
Aortic valve replacement	27
Redo aortic valve replacement	1
Multiple-valve replacement or repair	4
Atrial septal defect closure	1
Cor triatriatum + mitral valve replacement	1

CABG = coronary artery bypass grafting; LIMA = left internal mammary artery.

Delivery of cardioplegia through the coronary sinus route is not a new technique [21]. Different solutions have been used, such as intermittent cold crystalloid or blood cardioplegia, delivered through different routes, such as direct cannulation and snaring of coronary sinus ostium and bicaval cannulation and snaring with infusion into the right atrium with the aorta and pulmonary artery clamped. Drinkwater and co-workers [4] simplified the technique for catheter placement in the coronary sinus, which is now done in a closed fashion (ie, blindly) through a pursestring in the right atrium (usually without the need of bicaval cannulation or snaring) using a catheter with a self-inflating balloon.

We believe this is one of the first reports of the use of continuous warm blood cardioplegia through the coronary sinus. In this preliminary experience, the safety and effectiveness of the technique appear to be demonstrated. This technique allows performance of any kind of cardiac operation (except operation for anomolous coronary sinus) without the need of a single period of ischemia. The technique has been applied for coronary artery disease, valvar disease, congenital conditions, and combined operations (valve procedure and coronary artery bypass grafting) with excellent results. Additional animal and clinical studies are currently underway in our laboratories to further delineate the effects of warm continuous oxygenated blood cardioplegia through the coronary sinus route.

In our series of patients, 22% were more than 70 years old, and 39% were in New York Heart Association class IV. Also, of the patients undergoing bypass grafting, 51% had urgent revascularization. The preliminary clinical results in this difficult group of patients suggest that retrograde continuous warm blood cardioplegia may be a promising technique for high-risk operations.

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Coronary Pathology Predicts Conduction Disturbances After Coronary Artery Bypass Grafting

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Conduction disturbances after coronary artery bypass grafting may result from compromised septal blood flow. To examine this hypothesis we reviewed the preoperative coronary angiography of 55 consecutive patients undergoing coronary artery bypass grafting. Thirty-five patients had either no lesion or a discrete lesion in the left anterior descending coronary artery that did not include the septal perforator (type I anatomy). Twenty patients had a lesion of the left anterior descending coronary artery at the origin of the first septal branch, a lesion of the first septal artery, or a pair of lesions in the left anterior descending coronary artery that straddled the origin of the first septal artery; all lesions were proximal to the graft site (type II anatomy). None of the patients with type I anatomy had a major conduction disturbance after coronary artery bypass grafting. Eleven of the patients with type II anatomy had major conduction disturbances after coronary artery bypass grafting; right bundle-branch block in 1, right bundle-branch block and left anterior hemiblock in 2, left bundle-branch block in 5, and complete atrioventricular block that required pacemaker implantation in 3 ($p < 0.001$). In the 20 patients with type II anatomy, the appearance of conduction disturbances correlated well with the absence of retrograde flow to the septal branches from the right coronary artery ($p < 0.01$). Pathological lesions in the left anterior descending coronary artery that compromise flow in the first perforator and that do not provide an adequate circulation produce localized damage and conduction disturbances after coronary artery bypass grafting. This can be predicted from the preoperative angiographic anatomy.

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Conduction disturbances (CD) after coronary artery bypass grafting (CABG) are well known and occur with an incidence of 4% to 34% [1–4]. Improved myocardial preservation and the use of cardioplegia has decreased the incidence of intraoperative myocardial injury [5, 6]. Nonetheless, the incidence of postoperative CD has remained high [4, 7–10]. Cold potassium cardioplegia used today is associated with a 34% incidence of right bundle-branch block (RBBB) (often temporary) compared with 6% in a control group using ischemic arrest and intermittent perfusion [11]. The suggestion that CD are induced by global ischemia during CABG is probably too simplistic.

The present study was undertaken to determine whether there is a specific anatomical group of patients who are at risk for postoperative CD after CABG. We studied 55 consecutive patients who underwent open heart operations.

Patients and Methods

Three hundred twenty-nine patients underwent their first coronary artery bypass graft operation in the Surgical Department at Hadassah Hospital during a 3-year period. Of them, 55 consecutive patients were referred from the Cardiological Department in Hadassah Hospital. These patients are the subjects of the present study. Patients who also had aneurysmectomy, ventricular septal defect repair, or valvar operation were not included.

All patients underwent coronary artery bypass grafting under general anesthesia. Cardiopulmonary bypass was instituted with a bubble oxygenator. Myocardial preservation was achieved by core cooling to 24° to 26°C. St. Thomas' cardioplegic solution (1,400 to 2,500 mL per patient) was delivered through the ascending aorta. Cardiac and septal temperatures were monitored and were in the range of 8° to 15°C. Supplemental cardioplegia was delivered through vein grafts and the ascending aorta every 30 minutes. The heart was further cooled with topical iced saline solution. The following preoperative and perioperative details were noted: age, sex, previous myocardial infarction, cardiopulmonary bypass and aortic clamp time, perioperative myocardial infarction, old and perioperative conduction disturbances, and number and site of coronary bypass grafts.

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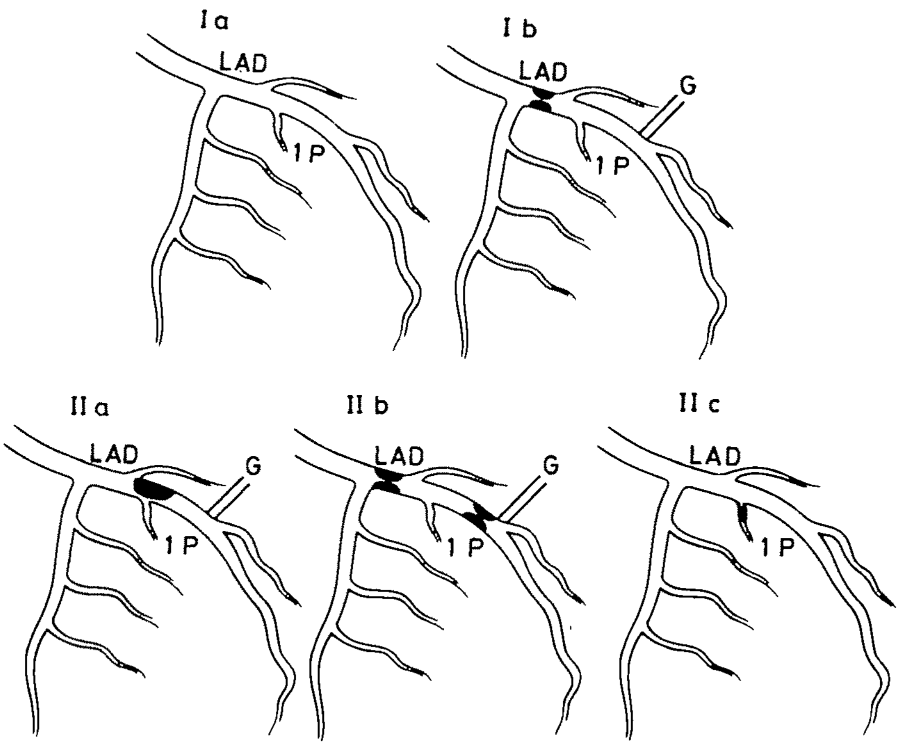

Fig 1. Classification of lesions in the left coronary system: type I, lesions not related to septal branches; type II, lesions related to septal branches (a, left anterior descending [LAD] *lesion at the origin of a septal branch; b, pair of LAD lesions straddling the septal artery; c, discrete lesion of the septal artery).* (G = *graft to LAD;* 1P = *first perforator.)*

Twelve-lead electrocardiograms were routinely recorded within 6 hours after operation and daily thereafter until discharge. Earlier electrocardiograms were recorded when the monitor was suggestive of ST-T changes or conduction disturbances. Blood creatine kinase examinations were performed in all patients with suspected myocardial infarction and in some patients with conduction disturbances without electrocardiographic evidence for myocardial infarction. Perioperative transmural myocardial infarction was diagnosed whenever a new Q wave unrelated to CD appeared in two leads in the electrocardiogram. A subendocardial wall infarction was diagnosed when ST-T changes (unrelated to CD and with no Q wave) appeared in any two leads and were accompanied with an increase in blood creatine kinase-MB level (>160 IU/L). Perioperative "major" CD were defined as complete right or left bundle-branch block (LBBB) or complete atrioventricular block. Conduction disturbances were persistent if they were still existing in the electrocardiogram at discharge. A postoperative thallium effort test (1 to 6 months after operation) to confirm or exclude septal hypoperfusion was available only in a minority of patients.

To increase the number of patients with postoperative CD, we analyzed the 11 of our consecutive 55 patients in whom CD developed and added another 12 patients with postoperative CD who had undergone angiography and operation in previous years. This created an extended group of patients with perioperative CD who were examined separately.

Coronary angiography was performed on a 4.5-inch General Electric image intensifier with an overframing lens to obtain maximum magnification. Angiograms were made in at least five different oblique projections including the craniocaudal projection. The coronary angiographic examinations performed before CABG were reviewed by a cardiologist who was blinded to the presence of CD. Lesions of more than 70% in one view were graded as serious. A detailed description of the lesions in the coronary arteries and their branches was drawn. Type I anatomy was defined as either no lesion (type Ia) or a discrete lesion in the left anterior descending coronary artery unrelated to the septal branches (type Ib) (Fig 1). Type II anatomy was defined as a lesion of the left anterior descending coronary artery (LAD) at the origin of a septal branch (IIa), a pair of lesions in the LAD straddling the septal artery (IIb), or a discrete lesion of the septal artery (IIc) all proximal to the graft anastomosis (Fig 1). Retrograde filling of the septum and the perforating arteries from the right coronary system was assessed qualitatively as good, moderate, poor, or none.

All continuous data were presented as mean ± standard deviation. The correlation between the anatomical types and the CD and between CD and retrograde filling of the septal arteries were tested by the Fisher's exact test. A comparison of the number of grafts in the two anatomical groups was performed using Student's *t* test.

Results

We studied 55 patients, 48 men and 7 women. Their mean age was 59 ± 7 years (range, 46 to 70 years). Thirty-five patients (age, 60 ± 4.7 years) had type I anatomy; 14 had type Ia and 21 had type Ib. Twenty patients (age, 58.2 ± 6.6 years) were found to have type II anatomy. Of these, 3 patients had type IIa lesions, 8 patients had a type IIb lesion, and 5 patients had type IIc lesions. Four patients had both type IIb and IIc lesions. Twenty-nine of the 35 patients with type I anatomy and 19 of the 20 with type II anatomy were male.

Correlation Between Conduction Disturbances and Pathological Anatomy

None of the 35 patients with type I anatomy had postoperative CD. Of the 20 patients with type II anatomy, 11 (55%) had major postoperative CD ($p < 0.001$). Only 1 patient with type II anatomy had preoperative CD (RBBB + left anterior hemiblock [LAHB]). After CABG he had temporary complete atrioventricular (AV) block that did not require permanent pacemaker implantation. No patient with type I anatomy had preoperative CD. Four patients with type I and 1 patient with type II anatomy had left main coronary disease (>40% narrowing), and none had CD.

Correlation Between Retrograde Filling of Septal Branches and Conduction Disturbances

Of patients with type II anatomy, 6 of the 9 patients without CD and only 1 of the 11 with CD had moderate or good retrograde filling of the septum from the posterior interventricular branch of the right coronary artery ($p < 0.01$). In patients with type I anatomy, 16 of 35 patients (all of them with type Ib) had moderate or good retrograde filling.

Types of Conduction Disturbances in Type II Anatomy

Eleven of the 20 patients with type II anatomy had one or more CD. Four of them had permanent LBBB, one had permanent RBBB, two had permanent RBBB and LAHB and 2 had permanent complete AV block that required implantation of a permanent pacemaker. Another patient had temporary LBBB that was followed by permanent LAHB, whereas another had temporary complete AV block requiring a permanent pacemaker implantation.

Correlation Between Previous Myocardial Infarction and Conduction Disturbances

One patient of 18 with a previous inferior myocardial infarction, 1 of 12 with previous anterior wall infarction, and 1 of 4 with both previous inferior and anterior myocardial infarctions had a major conduction disturbance. Three of the 21 patients with no previous myocardial infarction had major CD (p = not significant [NS]).

Distribution of Conduction Disturbances in the Extended Group

In the extended group with CD, 20 of 23 patients had type II anatomy. Their CD included complete AV block in 10 patients (temporary in 2), LBBB in 9 patients (temporary in 3), and RBBB in 4 patients. Four of them had LAHB and 1 had left posterior hemiblock. Three of the 23 patients had complete AV block (temporary in one) and type Ib anatomy and in all 3 there was no retrograde flow to septal branches. In 1 of them there was a 90% left main coronary artery lesion and in another total LAD coronary artery occlusion proximal to the first perforator. Other CD did not appear in patients with type I anatomy.

Correlation Between Operative Technique and Conduction Disturbances

The cardiopulmonary bypass time was 107 ± 22 minutes in type I anatomy and 111 ± 24 minutes in type II anatomy (p = NS). The aortic cross-clamp time was 53 ± 12 minutes in the group with type I anatomy and 57 ± 9 minutes in the group with type II anatomy (p = NS).

Correlation Between Anatomy Type and Number of Grafts

The average number of grafts in the group with a type I lesion was was 2.8 ± 0.6 and in the group with type II, 3.2 ± 0.6 (p = NS).

Correlation Between Conduction Disturbances and Number of Grafts

The 11 patients with CD had 3 ± 0.4 grafts per patient and the 44 patients without CD had 2.8 ± 0.6 grafts per patient (p = NS).

Correlation Between Perioperative Acute Myocardial Infarction and Anatomical Type

Five patients with type I anatomy had myocardial infarction (2 subendocardial and 3 transmural) without CD. Two patients with type II had myocardial infarction (one subendocardial anterior and one transmural lateral) without CD (p = NS).

Blood creatine kinase-MB level was examined in 4 patients with CD (all had complete AV block); it was increased in 2 and normal in the remaining 2.

Results of a postoperative thallium effort test were available in 6 patients. In 5 of them (4 with type I anatomy) it did not show septal hypoperfusion, and these patients did not have CD. The sixth patient had a reversible septal hypoperfusion and a large fixed defect in the inferoposterolateral wall. This patient had type IIa anatomy with no retrograde filling of septal branches, and after operation he had new permanent LBBB.

Comment

Preoperative and perioperative factors that have been investigated to determine the cause of CD include previous CD, left ventricular function, previous digitalis therapy, previous myocardial infarction, number of grafts, and the duration of cardiopulmonary bypass and aortic clamp time. Some workers found a positive correlation, but this was not confirmed by others. The relevant literature is summarized in Table 1.

Several anatomical data of the coronary arteries have been investigated and related to post-CABG conduction disturbances: the number of diseased coronary arteries was not found to be predictive [4, 8] but a correlation between RBBB and triple-vessel disease has been described [9]. Total occlusion of the LAD or right coronary artery [4, 8] or occlusion of both arteries [4] were unrelated to CD. Recently, RBBB and LAHB were found to be common in patients with left main coronary artery disease [4].

The present study was undertaken to determine the anatomical basis for predicting post-CABG CD. The prox-

Table 1. Perioperative Factors in the Genesis of Postoperative Conduction Disturbances as Described in the Literature

Factor	Relationship Positive	 None
Preoperative		
Previous conduction disturbances		[8]
Left ventricular function		[4]
Digitalis	[7[a]]	
Old anterior wall infarction	[7[a]]	[9]
Old inferior wall infarction	[4, 7[a], 9[a]]	
Angiographic characteristics		
Left main coronary artery disease	[4]	
Triple-vessel disease	[9[a]]	[4, 8]
Combined LAD and RCA disease		[4]
Operative		
Cold potassium cardioplegia	[11[b]]	
Number of grafts	[8]	[7]
Cardiopulmonary bypass time	[1, 8]	[4, 7]
Aortic clamp time	[1, 8, 9[a]]	[4, 7]

[a] Related to right bundle-branch block. [b] Related to temporary conduction disturbances.

LAD = left anterior descending coronary artery; RCA = right coronary artery.

imal bundle branches are located in the upper interventricular septum and are supplied by the first perforating branch of the LAD artery. It is obvious that a normal LAD is unrelated to postoperative CD. In contrast, we found that discrete lesions of the LAD (even when severe) that do not include the origin of the perforating branch did not put the patient at risk. In this anatomical subset (type Ib) coronary blood flow to the septal branches is maintained from the native coronary artery or the graft. On the other hand, in type II lesions, flow to the septal branches is compromised. The lesions are more important when retrograde flow from the right coronary artery to the septal branches is poor or absent. The damage to the conduction system in these cases may appear in this locus minoris resistentia during the period before or after aortopulmonary bypass if flow decreases and is inadequate or if cardioplegia is imperfect or prolonged. The combination of the coronary anatomy type with the operative technique may thus be important. Even if cardiopulmonary bypass is optimal, the improved flow from the graft may increase the perfusion pressure in the distal LAD and thereby decrease competitive flow proximal to the LAD graft including the perforator branch. Indeed, progression of proximal artery disease is accelerated in grafted arteries [12] and may be due to decreased laminar flow proximally to the graft. Good septal collateral flow, however, may prevent CD.

The differentiation between type I and II anatomy is straightforward. Because anatomical patterns ranging from a single large proximal septal perforator to a multitude of smaller septal vessels do exist, the subclassification in group II is sometimes more difficult; in a diffusely diseased LAD system with very little or no flow in the septal branches, it is difficult to decide what was the original size of the perforator arteries. Also, some of the patients were classified as having combined IIb and IIc lesions. Such anatomical differences between patients may contribute to the type, severity, and permanence of CD manifested in an individual patient. However, because the difference in rate of CD was found between anatomy types I and II, the results should not be altered.

The most frequent conduction disturbance was LBBB followed by complete AV block and RBBB. Similar findings were noted when the extended group of patients with CD after CABG was examined. The relatively low frequency of RBBB may be related to the good blood supply to this bundle both from the left and right coronary systems. For RBBB to occur, one needs compromised flow to both systems. However, we did not find a significant difference in the frequency of previous inferior or anterior myocardial infarctions in patients with CD. Three patients in the extended group had CD despite type I anatomy. One of them had left main coronary artery disease and another had total LAD occlusion proximal to the first perforator. Occlusion of the graft to the LAD may be the reason for the CD, but none of the patients was recatheterized to support this suggestion. It is also possible that intraoperative factors played a greater role in these patients. Notably, we did not find a correlation between left main coronary lesions and CD as suggested by others [4].

No correlation was found between CD and sex or age. However, the male predominance and the narrow range of age in both anatomy types preclude definite conclusions. No correlation was found between CD and the number of grafts, aortic clamp time, and cardiopulmonary bypass time. In 4 of the patients with CD (complete AV block), the level of creatine kinase-MB was examined. It was increased in 2 and normal in 2. Two patients with type II anatomy had electrocardiographic and enzymatic evidence of perioperative acute myocardial infarction but neither had CD. In addition, 5 patients with type I anatomy (and no CD) had perioperative myocardial infarction. Thus, the CD are not related to acute myocardial infarction in general, but rather to localized ischemia in the region of the first perforating branch, which supplies the conduction system. The information obtained by thallium effort test, in the few patients tested, agreed with the concept presented here to correlate between CD and septal vascularization. Because this study is retrospective and anatomy may have been changed since operation, we did not perform a thallium test on every patient.

Two practical implications may be derived from this study. First, intraoperative angioplasty, endarterectomy, or septal artery grafting should be considered in patients with type II lesions. Second, patients with type II anatomy undergoing CABG require more prolonged monitoring because CD may develop in them and require further interventions such as pacemaker implantation.

In conclusion, CD after CABG were found to be related to specific anatomical lesions involving the first perforating artery, which supplies the interventricular septum. Good retrograde filling of the septal branches from the right coronary artery before operation protects the heart against postoperative CD. Patients who have anatomical lesions involving the first perforating artery need a direct graft to the first perforating artery, endarterectomy, or intraoperative dilation of the offending lesion.

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Aggressive Surgical Intervention in N2 Non–Small Cell Cancer of the Lung

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An aggressive attitude toward surgical treatment was taken in patients with N2 non–small cell lung cancer in the past 10 years. Computed tomographic scanning was employed in the diagnosis of N2 disease, and had a true-positive rate of 57%. Among patients with N2 disease detected by computed tomographic scanning, surgical intervention was attempted except for those with unresectable disease. Of 190 patients with clinical N2 disease, 115 underwent surgical exploration: 9 patients had only an exploratory thoracotomy, 53 patients underwent a curative operation, and 53 had a noncurative operation. The overall 5-year survival rate of these patients was 16% and that of curatively resected patients was 20%. There were 47 patients whose N2 disease was not recognized before operation. The 5-year survival rate of this group was 20% overall and 33% in curatively resected cases. The overall 5-year survival rate of patients with N2 disease who underwent resection (106 with clinical N2 disease and 47 with clinically unrecognized N2 disease) was 17%, and that of the 84 patients undergoing curative operations was 24%. An aggressive attitude toward surgical intervention can be advocated for patients with N2 disease on the basis of our present results.

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Surgical treatment is the only method that holds the promise of long-term survival for patients with non–small cell lung cancer, and the role of the surgeon is to select appropriate surgical candidates so as to ensure the greatest possible benefit to the individual cancer patients. There are differences of opinion regarding the indications for operation in patients with ipsilateral mediastinal lymph node metastasis (N2 disease) discovered at thoracotomy. Some authors insist that all patients having preoperatively detected N2 disease should not be operated on. Others say that surgical candidates who may have N2 disease should undergo mediastinoscopy and that those with histologically proven N2 disease should be excluded from thoracotomy [1–6]. In contrast, there are some authors who believe that N2 disease does not contraindicate surgical resection [7–9].

Recently, Shields [10] reported on the significance of N2 disease in non–small cell lung carcinoma. He collected and analyzed many papers on the results of treatment in patients with N2 disease and concluded that a small subset of patients with resectable N2 disease discovered at thoracotomy or mediastinoscopy should be considered as potential surgical candidates. Unfortunately, the survivors from this group of patients represent only 3% to 6% of all patients with N2 disease, so N2 disease must be considered to have a very poor prognosis.

It has been our policy that all patients with marginally resectable N2 non–small cell lung carcinoma should be carefully evaluated with the possibility of surgical therapy in mind. As an operative procedure for N2 disease, extensive mediastinal lymph node dissection with some modification of the standard operation was done in the past 10 years. As a result, aggressive resection has been performed in patients with N2 disease whenever it was thought to be feasible after the preoperative work-up. At our institution, the routine use of computed tomographic (CT) scanning in the preoperative evaluation of N2 disease was started in 1980. This paper reports a clinical analysis of patients having N2 disease detected by preoperative CT scanning, by thoracotomy, or by postsurgical analysis of the resected specimens.

Material and Methods

Since 1980, all admitted lung cancer patients were examined by chest CT scanning to evaluate their T and N factors. In addition, evaluation of metastases to the brain, bone, and abdominal organs was performed by CT scanning, radioisotope scanning, and ultrasonography. Lymphadenopathy was routinely investigated by CT scanning and mediastinal lymph nodes larger than 10 mm along their short axis (except for subcarinal nodes) were defined as metastatic lymph nodes (N2 disease). For subcarinal lymph nodes, nodes larger than 15 mm along their short axis were defined as metastatic nodes. Calcified lymph nodes were not defined as metastatic nodes, even if their sizes fulfilled the criteria for N2 disease.

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Table 1. Patients With Clinical N2 Disease and Their Postoperative Diagnoses

Clinically N2 (n = 278)	Curative Operation	Noncurative Operation	No Resection[a]	Total
Postoperatively N0 (n = 50)				
T1–2 N0 M0	36	1	0	37
T3 N0 M0	6	0	0	6
T4 N0 M0	4	1	0	5
T2 N0 M1	0	2	0	2
Postoperatively N1 (n = 26)				
T1–2 N1 M0	15	2	0	17
T3 N1 M0	4	2	0	6
T4 N1 M0	2	0	0	2
T3 N1 M1	0	1	0	1
Postoperatively N2 (n = 190)				
T1 N2 M0	12	5	1	18
T2 N2 M0	24	11	10	45
T3 N2 M0	12	14	20	46
T4 N2 M0	5	7	7	19
T1 N2 M1	0	1	0	1
T2 N2 M1	0	3	9	12
T3 N2 M1	0	9	31	40
T4 N2 M1	0	3	6	9
Postoperatively N3 (n = 12)				
T1–2 N3 M0	0	4	0	4
T3 N3 M0	0	3	0	3
T4 N3 M0	0	3	0	3
T2 N3 M1	0	1	0	1
T3 N3 M1	0	1	0	1
Total	120	74	84	278

[a] Nine patients with exploratory thoracotomy without resection were included. Staging of patients not undergoing resection was performed clinically.

From 1980 to June 1990, 729 patients with proven non–small cell lung cancer were admitted to the Department of Surgery at Kanazawa University School of Medicine. All patients underwent CT scanning for evaluation of the N factors and the other factors needed for staging of the disease. There were 278 patients who were clinically diagnosed as having N2 disease (cN2) by preoperative CT scanning (Table 1). Among the patients who were shown to have N2 disease by preoperative CT scanning, surgical intervention was attempted, except in the following cases: patients with distant metastases to extrathoracic organs; patients with unresectable T4 lesions, such as malignant pleural effusion, or extensive invasion of the great vessel, vertebral bodies, trachea, or carina; patients with bulky N2 disease; and patients regarded as unsuitable for other reasons. Among the 278 cN2 patients, 203 were operated on and 194 (70% of cN2 patients) underwent resection. Nine patients only had an exploratory thoracotomy because of the extensiveness of their disease. On pathological examination of the resected specimens, 115 patients still had N2 disease (postsurgical histopathological N2, pN2), comprising 57% (115/194) of the N2 patients undergoing exploration.

If N2 disease that was not detected by preoperative CT scanning was discovered at thoracotomy by examination of frozen section, resection still proceeded unless other unresectable disease existed. After operation, all of the dissected lymph nodes were sent for pathological examination [11]. There were 47 patients whose preoperative diagnosis was N0 or N1, but who were verified to have N2 disease by intraoperative or postoperative pathology studies (Table 2).

A total of 153 pN2 patients have been accumulated in the past 10 years: 106 patients were cN2 patients and 47 were cN0 or cN1 patients. In addition, there were 83 cN2 patients in whom resection was not performed. Although N2 disease could not be verified by pathological examination in these unresected cases, they were defined as having actual N2 disease. The histology of these 236 N2 patients is shown in Table 3.

Routine systematic dissection of the mediastinal lymph nodes was performed in every case (even if the preoperative evaluation was N0 or N1), in accordance with the lymph node map proposed by the Japan Lung Cancer Society [12]. On the right side, the mediastinal pleura was longitudinally incised along the trachea and esophagus from the apex to the base of the right hemithorax. For node dissection in the superior mediastinum, the azygos vein was cut to mobilize the trachea, esophagus, and superior vena cava. All of the accessible lymph nodes in the superior mediastinum, ie, the superior mediastinal (#1), paratracheal (#2), pretracheal (#3), retrotracheal (#3p), and tracheobronchial angle (#4) nodes, were removed with the surrounding fat pad. The node anterior to the superior vena cava (#3a) was also routinely removed,

Table 2. Preoperative Staging of 47 Patients With Postoperatively N2 Disease That Was Not Detected by Preoperative Evaluation

Preoperative Staging	Curative Operation	Noncurative Operation	Total
Stage I			
T1 N0 M0	7	2	9
T2 N0 M0	11	3	14
Stage II			
T2 N1 M0	9	2	11
Stage IIIA			
T3 N0 M0	2	5	7
T3 N1 M0	2	1	3
Stage IIIB			
T4 N0 M0	0	2	2
T4 N1 M0	0	1	1
Total	31	16	47

Table 3. Histological Diagnosis and Operative Radicality of 237 Patients With N2 Disease

Diagnosis	Adenocarcinoma	Epidermoid Carcinoma	Adenosquamous Carcinoma	Large Cell Carcinoma	Mucoepidermoid Carcinoma	Total
Clinically N0–1 (n = 47)						
Curative operation	18	11	2	0	0	31
Noncurative operation	9	3	4	0	0	16
No resection	0	0	0	0	0	0
Clinically N2 (n = 190)						
Curative operation	22	25	2	2	2	53
Noncurative operation	27	19	5	2	0	53
No resection	48	30	0	5	1	84
Total with N2 disease (n = 237)						
Curative operation	40	36	4	2	2	84
Noncurative operation	35	23	9	2	0	69
No resection	48	30	0	5	1	84
Total	123	89	13	9	3	237

including thymic tissue. By these procedures all of the lymph nodes and fat pad located around the subclavian artery, trachea, right main bronchus, ascending aortic arch, superior vena cava, and upper thoracic esophagus could be completely removed. For node dissection in the inferior mediastinum, the incised posterior mediastinal pleura was reflected and the pulmonary ligament was cut to expose the tracheal bifurcation, both main bronchi, the pericardium, and the lower thoracic esophagus. All of the lymph nodes in this compartment, ie, subcarinal (#7), paraesophageal (#8), and pulmonary ligament (#9) nodes, were dissected out with their surrounding fat pad.

On the left side, lymph node dissection in the inferior mediastinum was performed similarly to that on the right side, excluding subcarinal node dissection. However, in the superior mediastinum, there were great anatomical limitations on node dissection, in contrast to the right side. As the routine procedure before the present series, the mediastinal pleura was incised just beneath the aortic arch and the subaortic (#5), paraaortic (#6), subcarinal (#7), paraesophageal (#8), pretracheal (#3), and paratracheal (#2) nodes were removed as far as it was possible. However, in the present series, the operative procedure was modified to allow more complete dissection of the lymph nodes in the left superior mediastinum. When left-sided N2 lung cancer was diagnosed by preoperative CT scanning or discovered at thoracotomy, two kinds of adjunctive procedures were performed in addition to the previous dissection method. For the earlier half of this series, the aortic arch and part of the descending aorta were mobilized by cutting a few intercostal arteries to allow more extensive removal of the superior mediastinal nodes. By this procedure, lymph nodes 3, 4, and 3p were completely dissected. In the later half of this series, to allow a far more extensive node dissection, median sternotomy was performed after procedures in the left hemithorax had been completed using the left posterolateral approach [13]. By this procedure, nodes 1, 2, 3, 3a, 4, and 7 in the ipsilateral side and also mediastinal and hilar lymph nodes in the contralateral side could be completely dissected.

For the comparison of surgical results, operative radicality was divided into two categories. Curative operations were defined as those in which the tumor and accessible mediastinal lymph nodes were completely removed, whereas noncurative operations were those in which the tumor, metastatic lymph nodes, or both were incompletely excised. Staging of all the patients was performed using the new TNM classification proposed by the Union Internationale Contre le Cancer in 1986 [14]. There exists disagreement regarding the definition of M1 disease in the case of intrapulmonary metastasis. The American Joint Committee defines pulmonary metastasis only to the contralateral lung as M1 disease [15], whereas the Union Internationale Contre le Cancer [14] and the Japan Lung Cancer Society [12] define both ipsilateral and contralateral pulmonary metastases as M1 disease. In this study, we adopted the latter definition. All of the 21 patients with postsurgical stage IV disease in the present series (see Table 1) had microscopic ipsilateral pulmonary metastases, which were discovered at postsurgical examination of the resected lung.

Radiation therapy was not done as routine postoperative treatment but was performed in some patients who underwent noncurative operations or in those in whom mediastinal nodal recurrence developed.

For calculation of the survival rate, we included six postoperative deaths occurring within 30 days of operation: all of them occurred in cN2-pN2 patients, with 3 being in the curative operation group and the other 3 in the noncurative operation group. The survival rate was calculated by the Kaplan-Meier method and statistical significance was evaluated by the Cox-Mantel and generalized Wilcoxon tests. When these two tests gave values of p less than 0.05, the difference was defined as statistically significant.

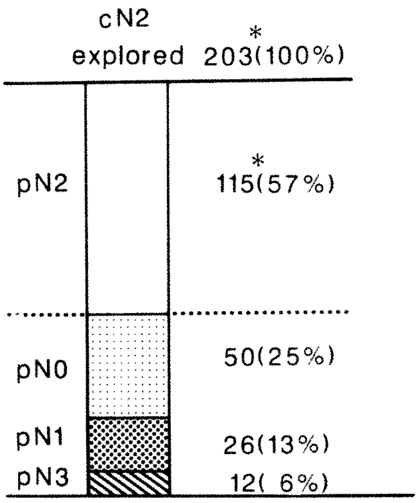

Fig 1. Postoperative staging of the N factor in 203 clinical N2 patients submitted for surgical exploration. (Nine patients having an exploratory thoracotomy were included.) (c = clinical stage; p = postoperative stage.)*

Results

Diagnostic Value of Preoperative Computed Tomographic Scanning in Assessing N2 Disease

This evaluation was made only in the resected non–small cell lung cancer patients, so 512 were eligible. The sensitivity, specificity, and accuracy of CT scanning in detecting N2 disease were 69%, 79%, and 76%, respectively. Predictive value of positive and negative tests were 58% and 86%, respectively. Among the 203 patients who were diagnosed to have N2 disease in the preoperative evaluation by CT scanning and underwent exploration, 115 patients (57%) had actual N2 disease, which was verified by postoperative histopathological examination (Fig 1). Another 50 patients (25% of explored cN2 patients) were pN0, 26 patients (13%) were pN1, and 12 patients were pN3, so the true-positive rate of CT scanning in the evaluation of N2 disease was only 57% and the false-positive rate was 39% among the explored patients.

Surgical Results in Clinically N2 Patients

Among the 278 patients who were diagnosed to have N2 disease by preoperative evaluation by CT scanning, there were 84 patients in whom resection was not performed, including 9 patients undergoing only exploratory thoracotomy due to extensive disease (see Table 1). The reasons in the 75 patients who did not undergo surgical intervention were as follows: distant metastasis, 46; malignant pleural effusion, 11; bulky N2 disease, 7; extensive invasion of mediastinal structures, 7; complications in major organs, 3; and refusal of operation, 2. The most common histological cell type in the nonresection group was adenocarcinoma (48/84), followed by epidermoid carcinoma (30/84) (see Table 3).

Excluding the 9 cases of exploratory thoracotomy, 106 patients with true N2 disease (cN2-pN2) underwent 53 curative and 53 noncurative operations (50% each) (see Table 1). When their cell types were compared, curative operation could be more frequently accomplished in patients with epidermoid carcinoma (25/44, 57%) than in those with adenocarcinoma (22/49, 44%). The survival curves of the patients in this group are shown in Figure 2. The 5-year survival rate of the patients with pN0 and pN1 disease were 68% and 53%, respectively. On the other hand, the 5-year survival rate of patients with pN2 disease was 16%, including six operative deaths, and it was 20% in curatively resected patients, including three operative deaths. There were significant differences between pN2 and pN0 disease, and between pN2 and pN1 disease, respectively. There were no 5-year survivors among the patients with cN2-pN2 disease who were incompletely resected, but 4 patients (3 with adenocarcinoma and 1 with adenosquamous carcinoma; 3 who underwent postoperative radiotherapy and 1 who did not) have survived more than 3 years after the operation.

Surgical Results of Clinically N0–1 but Postoperatively N2 Patients.

There were 47 patients whose preoperative stage was N0 or N1, but in whom N2 disease was discovered at thoracotomy or by postoperative pathological examination of the lymph nodes removed (see Table 2). Their preoperative evaluations of the N factor were N0 in 32 patients and N1 in 15 patients, and their preoperative staging was as follows: stage I in 23 patients, stage II in 11 patients, stage IIIA in 10 patients, and stage IIIB in 3 patients. Thirty-one patients (66%) underwent curative operations, and this rate was higher than that in patients with cN2-pN2 disease (50%). Noncurative operation was more common in the preoperatively stage IIIA and IIIB group than in those with stage I and II disease. Histological diagnoses for these 47 patients are shown in Table 3. Adenocarcinoma was the most frequent, followed by epidermoid carcinoma. Of the 47 patients, 31 had a curative operation and 16 had a noncurative operation. The survival curve of the 47 patients in this group is shown in Figure 3. The 5-year survival rate of this group overall (n = 47) was 17%, and it was 33% if the 16 patients who underwent noncurative operations (the longest survival was 38 months) were excluded.

Overall Surgical Results of Patients With Postoperatively N2 Disease

In all, there were 237 patients with N2 disease including 84 (35% of N2 patients) inoperable N2 patients (Fig 4). There were 153 resected patients (65%) with postoperatively N2 disease, and of these patients 106 had true-positive disease and 47 had false-negative disease on CT. Their histological diagnoses are shown in Table 3. Seventy-five had adenocarcinoma and 59 had epidermoid carcinoma. Eighty-four patients underwent curative operation (35% of N2 patients) and 69 had a noncurative operation. The survival curves are shown in Figure 5. The overall 5-year survival rate of the 153 patients was 17%, and that of the 84 patients undergoing curative operation was 24%. When the 5-year survival rates of the curatively resected patients with true-positive disease (n = 53) and

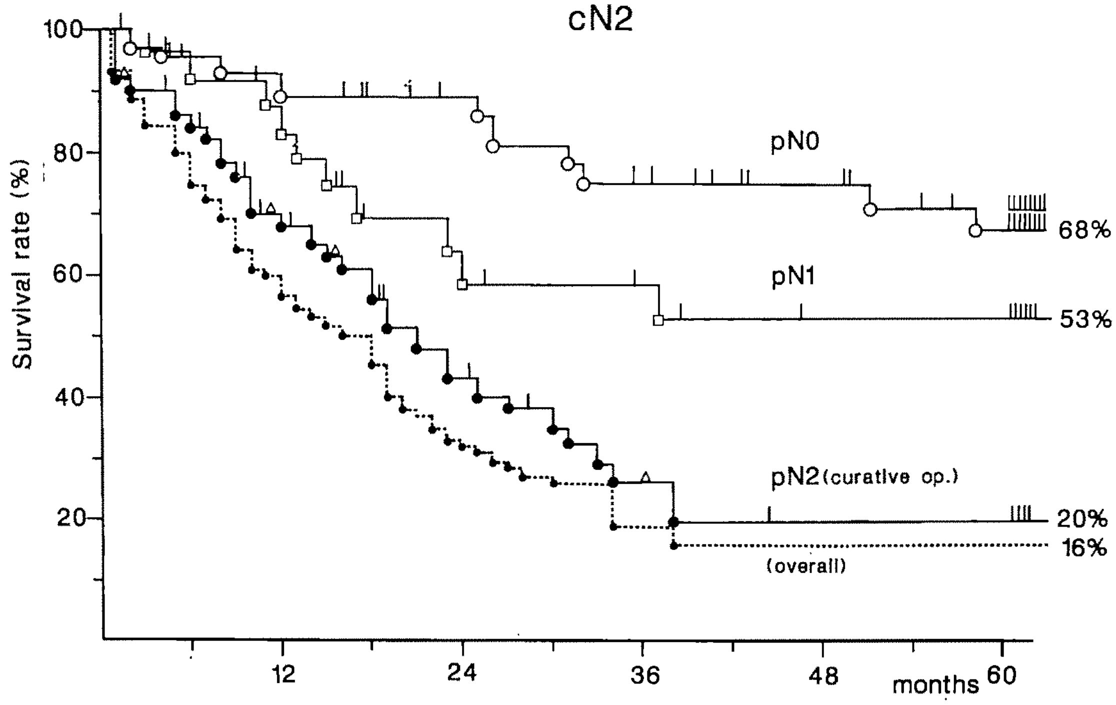

Fig 2. Survival curves of clinically N2 patients classified by the postoperative N factor. Operative deaths were included in the calculation of all survival rates in this and the other figures. (⊥ = alive with no evidence of disease; △ = dead with no evidence of disease; pN0 = *patients with clinical N2 disease but postsurgically N0 [n = 50];* pN1 = *patients with clinical N2 disease but postsurgically N1 [n = 26];* pN2 = *patients with clinical N2 disease and postsurgically N2 [n = 106].)*

those with false-negative disease (n = 31) on CT were compared, they were 20% and 33%, respectively, but there was no significant difference between the two groups.

The 5-year survival rates of the patients with adenocarcinoma (n = 40) and epidermoid carcinoma (n = 36) were 24% and 22%, respectively, showing no significant difference between the two. The 5-year survival rates of the

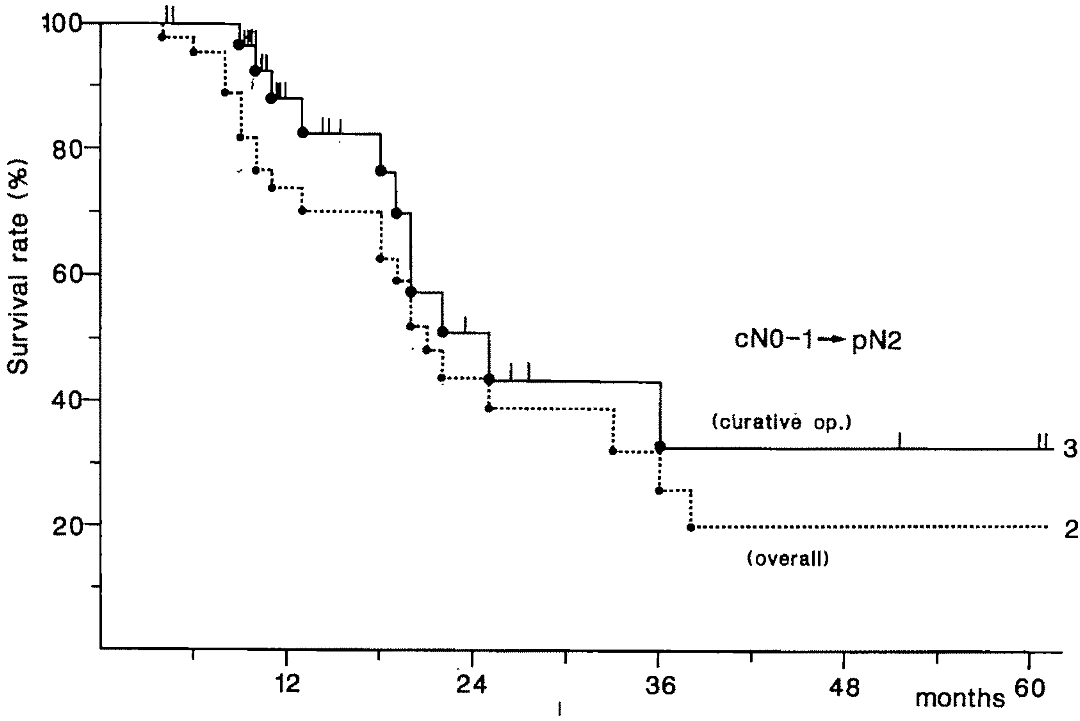

Fig 3. Survival curves of patients with clinically unrecognized N2 disease (clinical stage N0 or N1). (curative op. = *patients undergoing curative operation [n = 31];* overall = *patients undergoing curative operation plus those with noncurative operation [n = 47].)*

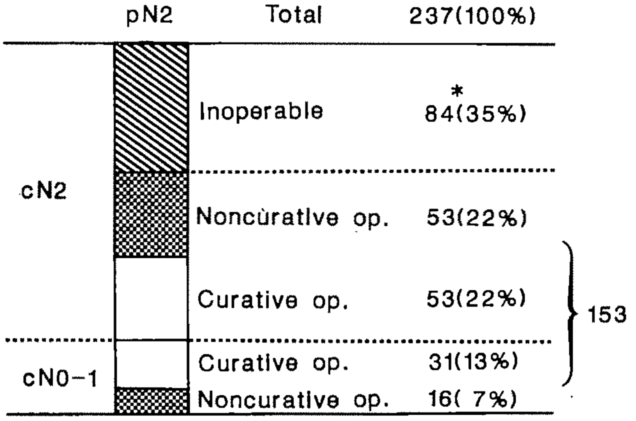

Fig 4. Distribution of 237 patients with N2 disease. (Nine patients undergoing exploratory thoracotomy were included.) (cN2 = patients with clinically proven N2 disease; cN0-1 = patients with clinically unrecognized N2 disease.)*

patients with T1 N2 M0 (n = 19) and T2 N2 M0 disease (n = 44) were 40% and 30%, respectively, whereas those of patients with T3 N2 M0 (n = 16) and T4 N2 M0 disease (n = 5) were 15% and 0, respectively. However, there were no significant differences between either T1 N2 M0 versus T2 N2 M0, T1 N2 versus T3 N2 M0, or T1 N2 M0 versus T3 N2 M0. Excluding T4 N2 M0 patients, a comparison was made in respect to number of metastatic levels (there were patients who had multiple metastatic lymph nodes within one level; however, they were calculated as one metastatic focus in this comparison). The 5-year survival rates of the patients with metastases confined within one level and those with metastases extending more than two levels were 35% and 7%, respectively, but there was no significant difference between the two groups.

Comment

A major factor affecting the prognosis of patients undergoing operation for lung cancer is the presence of lymph node metastases and their location. There should be no objection to the statement that definitive surgical treatment is the treatment of first choice for patients with stage I and II non-small cell lung cancer. However, there exists considerable controversy regarding the treatment of patients with mediastinal lymph node metastases. There are many physicians who do not regard surgical treatment as a valid option in patients with mediastinal node metastases, but we do not support this concept. Even among surgeons, there still exists controversy regarding the selection criteria for surgical intervention in patients with N2 disease [10, 16]. We have been taking an aggressive attitude toward surgical treatment in patients with mediastinal lymph node metastases. To allow more complete dissection of the mediastinal lymph nodes, extensive operative procedures have been applied in the past 10 years. As a result, there definitively was a group of patients with N2 disease who could undergo curative operations and gained long-term survival, even though it was a small part of the whole patient population with N2 disease.

In the preoperative evaluation of N2 disease, two alternative methods are used. One is noninvasive, using

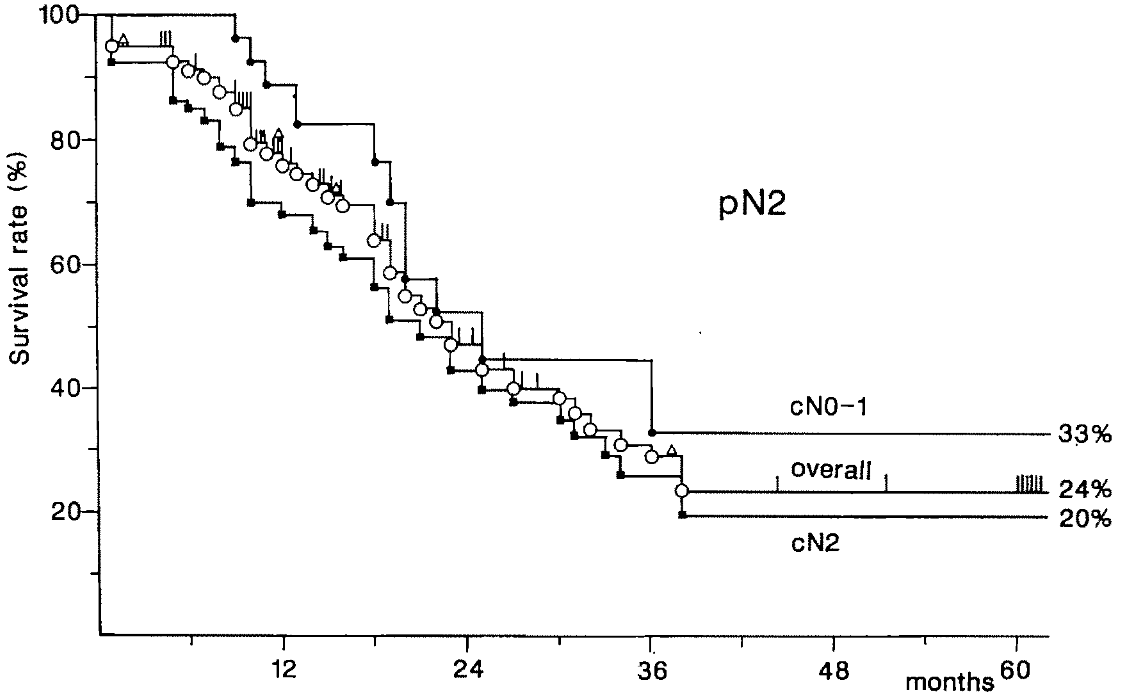

Fig 5. Survival curves of patients with N2 disease undergoing curative operation. (cN0-1 = patients with clinically unrecognized N2 disease [n = 31]; cN2 = patients with clinically proven N2 disease [n = 53]; symbols as in Figure 2.)

conventional tomograms, CT scanning, scintiscanning, or magnetic resonance imaging. The other is the use of invasive procedures, such as mediastinal exploration or mediastinoscopy. We did not employ mediastinoscopy, and CT scanning was used for the selection of our surgical candidates. Except for patients with bulky N2 disease, an aggressive attitude toward surgical intervention was taken, even if N2 disease was found preoperatively by CT scanning. It should be mentioned that the true-positive rate of CT in our present series was only 57% (115 of 203 explored patients), and the false-positive rate was 38%. Among these 115 explored cN2-pN2 patients, only 9 patients (7.8%) had a exploratory thoracotomy due to unresectable disease. If all the patients in our series with N2 disease detected by preoperative CT scanning were uniformly excluded from operation (as some physicians are doing), 39% of pN0 or pN1 patients would have been excluded. Because these patients have respective 5-year survival rates of 68% and 53% (including incompletely resected patients), they should not be denied the most appropriate treatment modality.

It should be remembered that the reported values of the sensitivity, accuracy, and predictive value of CT scanning in detecting N2 disease are relatively low, as was also observed in our present study. Whittlesey [17] employed CT scanning in the staging of lung cancer and reported that mediastinal lymph nodes larger than 2.0 cm were positive for tumor in 69.6%, nodes between 1.1 and 1.9 cm were positive in 31.8%, and nodes less than 1.0 cm were positive in 2.7%. He concluded that all patients with otherwise resectable disease and enlarged mediastinal lymph nodes (greater than 1.0 cm) should undergo surgical exploration before resection is ruled out, as the false-positive rate for enlarged nodes was significant. Moreover, Martini and Flehinger [9] have also reported that even when enlarged lymph nodes are found by CT scanning, many lung cancers are still resectable, and that more importantly, 20% to 30% of enlarged nodes detected by CT scanning are found to be hyperplastic and without metastasis. Magnetic resonance imaging has been expected to improve the accuracy of diagnosis of N2 disease, but Martini and associates [18] reported that there was no advantage of magnetic resonance imaging over CT scanning. Thus, both our present results and the data from these reports indicate that an aggressive attitude to surgical intervention is justified, even if lymphadenopathy is demonstrated in the mediastinum by preoperative CT scanning, provided that the suspected N2 disease is not unresectably bulky. There were only 7 patients with bulky unresectable N2 disease who did not undergo operation in our series.

Although the accuracy of preoperative diagnosis may be increased by the combined use of preoperative mediastinal exploration (eg, mediastinoscopy), we did not use mediastinoscopy as a routine method of preoperative investigation. Pearson and co-workers [1, 2] employed mediastinoscopy in selecting patients for surgical exploration and reported that the 5-year survival rate of the patients with N2 disease detected by mediastinoscopy (n = 79) was 9%. However, when mediastinoscopy was negative and N2 nodal involvement was found only at thoracotomy (n = 62), the actuarial survival rate was 24%. They did not mention the overall 5-year survival rate of their patients, but these results were not so different from those obtained in our series without mediastinoscopy in selection of surgical candidates (17% overall and 24% for curatively resected patients). Our data showed little difference in survival rates between patients whose N2 disease was detected before operation and those whose N2 disease was discovered at thoracotomy or by postoperative pathology studies, provided complete resection could be accomplished. We think, therefore, that bulky unresectable N2 disease can be satisfactorily detected by CT scanning alone, as there were only 9 patients found to be unresectable at thoracotomy.

Of course, there would be no objection to the use of mediastinoscopy in patient selection. Mediastinoscopy can be helpful in determining which clinically N2 patients may benefit from surgical exploration. However, there are some long-term survivors among mediastinoscopy-positive patients [1, 2]. Mediastinoscopy does not cover all the known lymph node stations, and it is not yet clear who is a surgical candidate among mediastinoscopy-positive patients. In some reports, all medistinoscopy-positive patients were not surgical candidates [3], whereas other authors have stated that mediastinal node metastasis without fixation in one station was no contraindication to exploration [4]. If all of mediastinoscopy-positive patients are uniformly excluded from operation, some patients who otherwise might be salvaged by surgical therapy will undergo inappropriate treatment.

Various results of surgical treatment of N2 disease have been reported. Pearson [1] collected the reported results of resection in patients with mediastinal lymph node metastases identified preoperatively and found a range from 0% to 20% for the 5-year survival rate. Survival of patients with N2 disease identified intraoperatively ranges from 0% to 30%, and is better than that of those with clinically evident N2 disease. We would like to emphasize that the surgical indications for N2 disease should not be discussed only on the basis of the reported survival rates, and that it is vital to make a correct interpretation of these confusing reports of the results of operation. It is worth noting that the patient populations vary greatly between institutions and that these differences are even more marked between Japan and western countries. The different results reported from Japan and western countries are thought to depend on the following reasons.

The first reason is a difference in the method of selection of patients with clinically proven N2 disease for operation. Many Japanese institutions (including our hospital) have a rather more aggressive attitude toward performing operation for clinically evident N2 disease than is evident in western countries. Second, our present series reports the experience of a surgical department, so most of the patients who had obviously inoperable disease (such as clinical evidence of metastasis to distant organs, hoarseness, superior vena cava syndrome, palpable supraclavicular lymph nodes, or other unresectable disease) were excluded from admission. Owing to these reasons, among the patients with clinically evident N2 disease, 106 of 190 patients (56%) underwent surgical resection. This rate is higher than that reported in the literature. Luke and colleagues [5] explored only 20% of 286 patients positive for N2 disease before thoracotomy, and Martini and Flehinger [9] explored 38% of 482 patients with clinically evident N2 disease. By the aggressive inclusion of surgical patients in our series, the ratio of resected patients with clinically proven N2 disease to all pN2 patients undergoing resection was increased. This could greatly bias the results of the overall surgical outcomes for N2 disease, because the rate of complete resection was much higher in the clinically unrecognized N2 group than in the clinically evident N2 group. If the number of patients with clinically evident N2 disease is much higher than the number with clinically unrecognized N2 disease (as it was in our series), the overall survival rate would be worse than if the series included a high incidence of patients with clinically unrecognized N2 disease. In our present series, the 153 pN2 patients undergoing resection comprised 106 (69%) with clinically evident N2 disease and 47 (31%) with clinically unrecognized N2 disease. In contrast, in Martini and Flehinger's series [9], the 403 pN2 patients undergoing resection comprised 179 (44%) with clinically evident N2 disease and 224 (56%) with clinically unrecognized N2 disease. When the survival rates were compared, the overall 5-year survival rate for the 153 pN2 patients in our series was 17%, which corresponded with the result of Naruke and associates [8] of 14% (n = 426). However, the 5-year survival rates for N2 patients reported by Mountain [7] and Martini and Flehinger [9] were 26%, and 30%, respectively. It must be remembered that both these reports gave the survival rates of the curatively resected group and not those of all patients, including the patients undergoing incomplete resection. The results for the 147 patients in Martini and Flehinger's [9] series with incomplete resection were not described, but they could greatly reduce the survival rate if the overall survival rate of resected patients were calculated. In addition, their series contained a rather small number of patients with detectable N2 disease, which generally shows a worse prognosis than clinically unrecognized N2 disease.

Another reason for the difference in the reported survival rate may concern the definitions of complete resection or curative operation. Martini and Flehinger [9] reported that the 5-year survival rate of patients with completely resected N2 disease was 30%, whereas the figures obtained by Naruke and associates [8] and in our present series were 20% and 24%, respectively. However, survival rates can be greatly modified by the selection of the complete resection group at the time of evaluating the survival data. In our present series, the frequency of curative operation in patients with clinically evident N2 disease was 28% overall and 46% of explored patients. The frequency of curative operation in the patients with clinically unrecognized N2 disease was 66%. In total, 84 of 153 N2 patients (55%) undergoing resection underwent curative operation (see Fig 1). In contrast, in the series of Martini and Flehinger [9], only 7% (32/482) of clinically recognized N2 patients and 18% (32/179) of explored patients underwent complete resection. Furthermore, even among the patients with clinically unrecognized N2 disease, only 119 out of 224 resected patients (53%) underwent complete resection. In all, only 38% (151/403) of their N2 patients undergoing resection had a complete resection procedure, a rate far lower than that in our series. The relatively high rate of curative resection in our present series might be partly due to our operative procedure of extensive mediastinal lymph node dissection, but there must also be some differences among these series in the definition of curative operation.

Mountain [7] reported a 26% 5-year survival in patients with completely resected N2 disease, and defined complete resection as being achieved when the most distal nodes within each major lymphatic drainage region are microscopically free of tumor. If the farthest node in the dissection is positive for tumor, they defined the resection as incomplete. This definition, although it is not described in detail, is markedly different from our definition [12]. We defined complete resection as a procedure in which all accessible metastatic lymph nodes were removed, even if the most distal node was found to be involved. If we use Mountain's criteria to define complete resection, a considerable number of our patients are then excluded from the complete resection group, which results in an improvement of the survival rate of the complete resection group. There is thus an urgent need for international agreement regarding the definition of operative radicality so as to allow a more rational comparison of the surgical results.

We have been adopting an aggressive attitude to clinically evident N2 disease, because the reported survival rates of nonsurgical treatment in patients with N2 disease were extremely low. The 3-year and 5-year survival rates of nonsurgically treated N2 patients in our series were 7% and 4%, respectively, and their 50% survival length was 6 months. Our present series supports the value of an aggressive attitude toward resection in patients with N2 disease. However, the results of surgical treatment of N2 disease shown by the present series were not satisfactory. To improve the resectability rate and ultimately the survival of patients with clinically evident N2 disease, neoadjuvant therapy has been attempted in several preliminary trials [19, 20]. We also have started such a clinical trial recently, but it is too early yet to make any clear conclusions regarding the survival rate. However, such therapy seems to improve the resection rate of bulky N2 disease.

In conclusion, an aggressive attitude toward surgical intervention for N2 disease can be advocated. In patients with N2 disease detected either by preoperative investigations or at thoracotomy, complete resection should be performed whenever possible by employing extended surgical procedures to allow complete dissection of the mediastinal lymph nodes.

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Dopamine and High-Dose Insulin Infusion (Glucose-Insulin-Potassium) After a Cardiac Operation: Effects on Myocardial Metabolism

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Myocardial insulin resistance, in association with surgical stress, restricts the availability of carbohydrates and increases the load of free fatty acids (FFAs) on the heart. On theoretical grounds adrenergic drugs may be expected to aggravate this situation, whereas the opposite is expected from insulin. The influence of dopamine and a combination of dopamine (7 μg/kg body weight/min) and high-dose insulin (7 IU/kg) on myocardial energy metabolism was studied in 19 patients 4 to 6 hours after a coronary operation. Infusion of dopamine (7 μg/kg body weight/min) induced metabolic changes that may be unfavorable to the strained myocardium. There was an increase of the myocardial FFA load and a rise in myocardial oxygen expenditure by 60% to 70%. These changes were, however, not matched by an increase in myocardial substrate uptake. "Oxygen wastage" of FFA metabolism at high circulating catecholamine levels is suggested. There were also signs suggesting an amplified systemic trauma response: systemic oxygen consumption increased by 15%, and an increase in the arterial levels of FFAs, glucose, and ketones was observed. Divergent metabolic effects of dopamine and insulin were demonstrated. The most prominent metabolic effects of adding high-dose insulin to dopamine were a marked reduction of arterial FFA levels and a shift toward myocardial carbohydrate utilization at the expense of FFAs. Myocardial uptake of FFAs ceased. Myocardial insulin resistance may thus to a significant extent be overcome by supraphysiological doses of insulin, even during infusion of adrenergic drugs.

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The heart is under the influence of the neuroendocrine response of trauma metabolism early after a cardiac operation. This leads to an increased load of free fatty acids (FFAs) and a severely restricted availability of carbohydrates for myocardial energy production [1]. Both these factors reflect insulin resistance and may adversely affect myocardial function and recovery after ischemia [2–4].

Inotropic, adrenergic agents are commonly used to improve low output states in the postoperative period of cardiac operations. These agents add to the increased cathecolamine levels of trauma metabolism and may put further strain on the already compromised energy metabolism of the heart. Only sparse data are available on the actual effects of adrenergic agents on myocardial uptake of substrates in this clinical situation. Our first aim was to investigate the myocardial uptake of substrates during the infusion of dopamine.

The infusion of large doses of insulin improves the hemodynamic state of patients after cardiac operations [5]. At the same time insulin modifies the effects of trauma metabolism in a direction that seems beneficial by reducing the FFA load on the heart and by increasing the availability of carbohydrates [1]. Although insulin may suffice in some patients with postoperative heart failure, other patients are likely to need additional inotropic therapy. As has been pointed out, insulin and dopamine have diverging metabolic effects. The net effect of the combined use of insulin and dopamine is not known. Our second aim was to study the metabolic effects of the simultaneous use of insulin and dopamine.

Material and Methods

Patients

Nineteen male patients, aged 40 to 65 years (mean, 56.3 ± 2.3), with stable angina pectoris and well-preserved left ventricular function (ejection fraction >0.50) admitted for elective aortocoronary bypass grafting were included in the study. None of the patients had diabetes mellitus or other major metabolic disorders. All patients were on long-term treatment with β_1-blocking agents with a last preoperative dose given 2 to 3 hours before the start of operation (Table 1).

Clinical Management

After an overnight fast the patients were premedicated with 10 mg of morphine hydrochloride and 0.4 mg of scopolamine intramuscularly. Anesthesia was induced with thiopentone and fentanyl. Neuromuscular blockade

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Table 1. Patient Data[a]

Variable	Dopamine	Insulin-Dopamine
Patient No.	10	9
Age (y)	56 ± 2	57 ± 1
Weight (kg)	80 ± 3	79 ± 2
Body surface area (m^2)	1.96 ± 0.04	1.96 ± 0.03
Grafted vessels	3.0 ± 0.3	3.0 ± 0.2
Cross-clamp time (min)	57 ± 5	57 ± 5
Extracorporeal circulation time (min)	113 ± 10	119 ± 8
Aspartate aminotransferase (μkat/L)	0.93 ± 0.11	1.08 ± 0.24

[a] There were no significant differences between groups.

was achieved with pancuronium, and anesthesia was maintained using fentanyl, N_2O in oxygen, and supplementation with either halothane, enflurane, or isoflurane.

Cardiopulmonary bypass was conducted with a bubble oxygenator and a roller pump generating nonpulsatile flow. Ringer's acetate was used to prime the extracorporeal circuit. Moderate hemodilution (hematocrit, 0.20 to 0.25) and hypothermia (30° to 32°C) were employed. St. Thomas' cold crystalloid cardioplegic solution was used for myocardial protection. Weaning off cardiopulmonary bypass was started at a rectal temperature of 36.5°C. Heparin was neutralized with protamine chloride until preoperative activated clotting time level was achieved.

Fentanyl analgesia (0.1 to 0.2 mg/h) and mechanical ventilation (inspired oxygen fraction was adjusted to keep arterial oxygen tension at 15 kPa) with a positive end-expiratory pressure of 5 cm H_2O were maintained during the study period. A stable left atrial pressure of approximately 12 mm Hg was sustained by infusion of blood or plasma according to the hematocrit, which was kept between 0.30 and 0.35.

According to our clinical routine, nitroglycerin was infused when systolic blood pressure exceeded 130 mm Hg in the "basal state." The infusion of dopamine increased blood pressure in most patients. A pressure increase up to 150 mm Hg was accepted, but at higher pressures a nitroglycerin infusion was begun, or if already in use, adjusted to obtain a pressure less than 150 mm Hg. Nine of 19 patients thus received nitroglycerin in the basal state. There was no difference between the groups regarding nitroglycerin requirement during the study periods.

Study Protocol

The patients were studied approximately 4 to 5 hours after completion of the operation, having passed the shivering phase and become hemodynamically stable. Further descriptive data are given in Table 2.

The patients were allocated into two groups, after randomization in blocks of six, to obtain an even sequential distribution. One group comprising 10 patients, referred to as the dopamine group, received dopamine (7 μg/kg body weight/min) over two 30-minute periods, separated by a 30-minute interval. The other group of 9 patients, the insulin-dopamine group, received dopamine (7 μg/kg body weight/min) over a first 30-minute period; after a 30-minute interval, dopamine (7 μg/kg body weight/min) was given in combination with a primed (injection of 1 IU/kg) high-dose insulin infusion (6 IU/kg body weight) over 30 minutes. Blood glucose level was monitored (AGM, Gambro, Lund, Sweden) and kept constant at the preinsulin level by adjusting the rate of infusion of a 40% solution of glucose (40 to 70 mL/h). In clinical practice, however, continuous monitoring of blood glucose is not necessary because moderate hyperglycemia is accepted (7 to 12 mmol/L). To maintain serum levels of potassium and phosphate at the preinsulin level, 100 mmol/L potassium and 30 mmol/L phosphate were included in the solution. Serum potassium level was checked every 30 minutes and levels down to 3.5 mmol/L were accepted to avoid rebound hyperkalemia at the withdrawal of glucose-insulin. After the infusion of insulin had been completed the glucose infusion was maintained for 8 to 12 hours and the infusion rate gradually decreased according to the level of blood glucose.

Measurements

Hemodynamic and biochemical measurements were performed (1) at the basal state, before the infusion of dopamine, (2) after 30 minutes' dopamine infusion (first infusion period), (3) after a 30-minute interval, and (4) after the second infusion period with either dopamine or insulin-dopamine (second infusion period).

Arterial blood pressure was measured in the radial artery. The right atrium, pulmonary artery, and left atrium were catheterized for measurement of central venous pressure, pulmonary arterial pressure, and left atrial pressure.

The electrocardiogram was continuously monitored from the V_5 lead (Siemens Elema Sirecust 404).

A Swan-Ganz catheter (7F, Edwards, CA) was used for measurement of cardiac output. A coronary sinus catheter (Webster Lab, CA) was inserted through the right internal jugular vein and its final midcoronary position was checked by fluoroscopy and measurement of oxygen saturation [6]. The patency of the catheters was maintained by saline infusion 3 mL/hour. Cardiac output and coronary sinus blood flow were determined by thermodilution techniques and calculated from the mean value of three observations. Because of technical difficulties coronary sinus blood flow measurements were not obtained in 2 patients (patients 10 and 19).

Hemodynamic measurements were followed by simultaneous blood sampling from the coronary sinus and radial artery for determination of blood gases and plasma concentrations of glucose, lactate, pyruvate, free fatty acids, glycerol, β-hydroxybutyrate, and amino acids. Due to technical errors and inadequate sampling volumes complete substrate data were not obtained from all patients. The number of observations for each substrate are denoted by *n* in the tables.

Plasma glucose level was determined as the median value of triplicate analyses. Blood for analyses of the other

Table 2. Hemodynamic Results

Variable	1	2	3	4
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.9 ± 0.2	3.9 ± 0.2^{b}	3.3 ± 0.2^{b}	
D	2.6 ± 0.1	3.6 ± 0.2^{b}	3.0 ± 0.2^{a}	3.7 ± 0.2^{b}
I	3.1 ± 0.3	4.2 ± 0.3^{b}	3.6 ± 0.3^{a}	$5.1 \pm 0.3^{b,d}$
HR (beats/min)	86 ± 2	102 ± 4^{b}	92 ± 2^{a}	
D	83 ± 4	100 ± 5^{b}	89 ± 4	103 ± 5^{b}
I	89 ± 3	104 ± 7^{a}	95 ± 3	110 ± 7^{b}
MAP (mm Hg)	81 ± 2	80 ± 3	70 ± 2^{b}	
D	82 ± 3	81 ± 5	70 ± 3	80 ± 4^{a}
I	80 ± 3	79 ± 3	69 ± 3^{a}	69 ± 3^{c}
CVP (mm Hg)	10 ± 1	10 ± 1	10 ± 1	
D	11 ± 1	9 ± 1	10 ± 1	10 ± 1
I	10 ± 1	11 ± 1	10 ± 1	10 ± 1
SVRI ($dyne \cdot s \cdot cm^{-5} \cdot m^{-2}$)	2110 ± 161	1492 ± 80^{b}	1530 ± 108	
D	2235 ± 188	1640 ± 91^{b}	1710 ± 156	1576 ± 86
I	1972 ± 274	$1345 \pm 116^{b,c}$	1350 ± 130	$945 \pm 65^{b,d}$
CSF (mL/min)	147 ± 12	164 ± 14	158 ± 14	
D	138 ± 9	144 ± 9	142 ± 17	180 ± 16^{a}
I	156 ± 22	182 ± 25	174 ± 22	242 ± 44^{b}
MVO_2 (mL/min)	11.0 ± 1.0	16.1 ± 1.7^{b}	10.5 ± 0.9^{b}	
D	11.2 ± 1.1	14.7 ± 1.0^{b}	10.3 ± 0.8^{a}	17.1 ± 1.5^{b}
I	10.8 ± 1.6	17.4 ± 3.0^{b}	10.7 ± 1.7^{b}	19.6 ± 4.1^{b}
VO_2 (mL/min)	239 ± 13	270 ± 17^{a}	247 ± 15^{a}	
D	228 ± 12	248 ± 11	247 ± 17	262 ± 10
I	251 ± 25	294 ± 33^{a}	248 ± 26^{b}	252 ± 16
Temp (°C)	37.7 ± 0.1	37.9 ± 0.1^{a}	38.2 ± 0.1^{b}	
D	37.7 ± 0.2	37.9 ± 0.2	38.1 ± 0.2^{b}	38.2 ± 0.1
I	37.7 ± 0.1	37.8 ± 0.1	38.0 ± 0.1	38.1 ± 0.1

Significant difference compared with observation obtained 30 minutes earlier within group: ^{a} $p < 0.05$; ^{b} $p < 0.01$. Significant difference between groups: ^{c} $p < 0.05$; ^{d} $p < 0.01$.

CI = cardiac index; CSF = coronary sinus blood flow; CVP = central venous pressure; D = dopamine group; HR = heart rate; I = insulin-dopamine group; MAP = mean arterial blood pressure; MVO_2 = myocardial oxygen consumption; SVRI = systemic vascular resistance index; Temp = rectal temperature; VO_2 = systemic oxygen consumption; 1 = basal state; 2 = after 30 minutes of dopamine infusion; 3 = 30 minutes after discontinuation of first dopamine infusion; 4 = after 30 minutes of either dopamine infusion or the combination of insulin and dopamine.

energy substrates and amino acids was immediately centrifuged and deep-frozen to less than -70°C until analysis.

Biochemical Analyses

Free fatty acids in serum were determined by a combined enzymatic and colorimetric method described by Shimizu and associates [7]. With this method a reddish complex formed during assay was monitored at 550 nm. The analyses were performed in special glass tubes because other material did not give satisfactory recovery. The coefficient of variation of the method at 1 mmol/L of FFA was 3.9%.

Lactate, pyruvate, and glycerol were all determined by coupled enzymatic reactions terminating in stochiometric redox-reactions of NAD/NADH. The coenzyme conversion from one state to the other was monitored at 340 nm. β-OH-butyrate, as a representative of ketone bodies, was estimated by enzymatic oxidation to acetoacetate, monitoring the concomitant reduction of NAD^{+} at 340 nm. Amino acids in serum were determined in samples treated with perchloric acid. The analyses were run on a Biotronic amino acid analyzer LC 2000 according to Moore and Stein [8]. Oxygen saturation and hemoglobin concentrations were measured in an OSM2 oximeter (Radiometer, Copenhagen, Denmark).

Calculations and Definitions

Left ventricular oxygen consumption was estimated as the product of arterial-coronary sinus blood oxygen content difference and coronary sinus blood flow. Myocardial flux of substrates was determined as the product of arterial-coronary sinus plasma concentration difference and coronary sinus plasma flow. An uptake of substrates was defined as a flux value significantly ($p < 0.05$) greater than zero, and a release of substrates was defined as a flux value significantly ($p < 0.05$) less than zero. Derived hemodynamic variables were calculated from standard formulas.

Table 3. Myocardial Flux of Substrates

Substrate	1	2	3	4
Glucose (μmol/min) (n = 17)	1.9 ± 6.7	−10.8 ± 6.7	−4.8 ± 7.1	
D	−6.8 ± 6.6	−14.6 ± 8.0	1.7 ± 11.2	1.6 ± 13.1
I	10.7 ± 11.2	−6.3 ± 11.7	−11.3 ± 8.9	40.9 ± 21.3^{b,c}
Lactate (μmol/min) (n = 17)	7 ± 12	−18 ± 31	−5 ± 13	
D	18 ± 16	−2 ± 15	8 ± 10	10 ± 12
I	0 ± 20	−39 ± 54	−18 ± 24	8 ± 25
Pyruvate (μmol/min) (n = 15)	0.9 ± 1.3	−0.8 ± 0.8	0.7 ± 0.4	
D	2.9 ± 0.8^{b}	−0.7 ± 1.0^{c}	1.0 ± 0.6	−0.8 ± 1.3
I	−1.4 ± 2.4	−0.9 ± 1.1	0.4 ± 0.5	10.8 ± 2.3^{b,d,e}
FFA (μmol/min) (n = 16)	31.8 ± 9.6^{b}	31.5 ± 5.1^{b}	30.6 ± 5.0^{b}	
D	27.6 ± 11.2^{b}	30.5 ± 7.4^{b}	23.4 ± 5.2^{b}	24.8 ± 4.3^{b}
I	37.3 ± 17.7^{b}	32.5 ± 7.4^{b}	37.8 ± 8.0^{b}	14.4 ± 14.2
β-OH-butyric acid (μmol/min) (n = 17)	0.5 ± 7.0	6.7 ± 3.6^{a}	6.5 ± 3.7^{a}	
D	7.3 ± 9.5	9.9 ± 7.1	6.2 ± 6.6	8.7 ± 5.2
I	−6.3 ± 10.3	3.9 ± 2.9	6.9 ± 4.0	6.8 ± 4.3
Glycerol (μmol/min) (n = 10)	−0.7 ± 1.3	−1.4 ± 0.4^{b}	−2.6 ± 1.6	
D	−0.3 ± 1.6	−0.5 ± 0.6	−1.8 ± 1.5	0.0 ± 1.3
I	−1.3 ± 2.3	−2.1 ± 0.4^{b}	−3.1 ± 2.8	−4.9 ± 2.6^{b,d}

Flux value significantly different from 0: ^{a} $p < 0.05$; ^{b} $p < 0.01$. Significant difference compared with observation obtained 30 minutes earlier within group: ^{c} $p < 0.05$; ^{d} $p < 0.01$. Significant difference between groups: ^{e} $p < 0.01$.

FFA = free fatty acids; all other abbreviations in Table 2.

Statistical Analyses

The protocol was designed to allow unpaired analyses between the insulin-dopamine group and the dopamine group, as well as paired analyses within each group. Statistical analyses were performed with a computerized statistical package (RS/1 BBN Inc, Cambridge, MA). Because of the small samples, nonparametric tests were used: the Wilcoxon test for matched pairs, the Mann-Whitney U-test for unpaired observations, and the Spearman rank test for regression analyses. Significance was defined as $p < 0.05$. Data are presented as mean ± standard error of the mean. The number of observations is denoted by n.

Ethical Aspects

The study was performed according to the principles of the Helsinki Declaration of Human Rights, and was approved by the ethics committee for medical research at the University Hospital of Uppsala. Informed consent was obtained from each patient.

Results

Clinical Course

The postoperative course was uneventful and no serious side effects of the drugs were seen. One patient in the insulin-dopamine group had a short period of frequent premature ventricular contractions, which only required adjustment of serum potassium level.

None of the patients showed any electrocardiographic signs of perioperative myocardial infarction, and postoperative aspartate aminotransferase levels on the day after operation averaged 0.93 ± 0.11 μkat/L in the dopamine group and 1.08 ± 0.24 μkat/L in the insulin-dopamine group.

Effects of Dopamine

HEMODYNAMIC VARIABLES (Table 2). Dopamine increased cardiac output by 39.6% ± 5.9% during the first infusion period. This was the result of equal increases of heart rate (19.1% ± 4.1%) and stroke volume (18.9% ± 6.1%). In the second infusion period cardiac output increased 25.9% ± 6.7%. Heart rate increased 15.4% ± 3.3% whereas stroke volume was unchanged (9.2% ± 5.5%).

MYOCARDIAL UPTAKE OF OXYGEN (Table 2). Myocardial oxygen uptake increased by 60.4% ± 19.2% during the first infusion and by 70.7% ± 15.6% during the second infusion. These changes were not parallelled by increases of coronary sinus blood flow, thus coronary sinus blood oxygen saturation decreased from 40.2% ± 1.2% to 25.5% ± 1.8% during the first infusion and from 42.5% ± 2.4% to 28.2% ± 2.3% during the second infusion.

MYOCARDIAL UPTAKE OF SUBSTRATES (Tables 3, 4). Dopamine infusion resulted in an increase of arterial plasma levels of FFAs from 832 ± 74 to 1,041 ± 81 μmol/L ($p < 0.05$) during the first infusion period and from 805 ± 99 to 852 ± 96 μmol/L ($p < 0.05$) during the second infusion period. Myocardial uptake of FFAs was unchanged. Arterial level of glycerol was unchanged and dopamine had no obvious effect on myocardial flux of glycerol.

Table 4. Myocardial Amino Acid Flux[a]

Amino Acid	1	2	3	4
Leucine	1.1 ± 0.3^{c}	0.9 ± 0.2^{c}	1.1 ± 0.1^{c}	
D	0.8 ± 0.3^{c}	0.9 ± 0.2^{c}	0.9 ± 0.2^{c}	1.1 ± 0.3^{c}
I	1.5 ± 0.5^{b}	0.9 ± 0.3	1.2 ± 0.2^{c}	1.2 ± 0.4^{c}
Isoleucine	0.3 ± 0.1^{c}	0.2 ± 0.1^{b}	0.3 ± 0.1^{c}	
D	0.2 ± 0.1^{c}	0.2 ± 0.1	0.2 ± 0.2	0.5 ± 0.3
I	0.4 ± 0.2^{b}	0.2 ± 0.1	0.3 ± 0.1^{c}	0.2 ± 0.2
Valine	1.1 ± 0.5^{b}	0.8 ± 0.3^{c}	0.7 ± 0.3^{b}	
D	0.4 ± 0.6	0.8 ± 0.4^{b}	0.6 ± 0.4	0.5 ± 0.5
I	1.7 ± 0.7	0.7 ± 0.4	0.8 ± 0.5	0.7 ± 0.5
Arginine	0.4 ± 0.2	0.4 ± 0.2^{b}	0.3 ± 0.2	
D	0.2 ± 0.2	0.5 ± 0.2	0.5 ± 0.4	-0.3 ± 0.4
I	0.6 ± 0.3	0.3 ± 0.2	0.0 ± 0.1	$1.1 \pm 0.4^{b,d,f}$
Methionine	0.1 ± 0.1	0.0 ± 0.1	-0.1 ± 0.1^{b}	
D	0.0 ± 0.1	0.0 ± 0.1	-0.1 ± 0.1	0.0 ± 0.0
I	0.1 ± 0.1	0.1 ± 0.0^{c}	$-0.1 \pm 0.1^{c,e}$	0.2 ± 0.1^{d}
Alanine	-1.0 ± 0.5^{b}	-2.2 ± 0.4^{c}	-2.3 ± 0.4^{c}	
D	-1.4 ± 0.7	-1.7 ± 0.4^{b}	-2.5 ± 0.5^{b}	-4.1 ± 1.6^{b}
I	-0.7 ± 0.7	-2.6 ± 0.7^{b}	-2.2 ± 0.7^{b}	-1.2 ± 0.9
Glutamine	-0.1 ± 1.1	-0.5 ± 0.5	-0.6 ± 0.2^{b}	
D	0.2 ± 1.4	-0.6 ± 0.7	-0.6 ± 0.3	-1.2 ± 0.7
I	-0.4 ± 1.7	-0.4 ± 0.8	-0.6 ± 0.3	-1.6 ± 1.6
Glutamate	2.3 ± 0.4^{c}	2.2 ± 0.3^{c}	2.7 ± 0.3^{c}	
D	2.2 ± 0.5^{c}	2.7 ± 0.3^{c}	2.9 ± 0.5^{c}	3.2 ± 0.5^{c}
I	2.4 ± 0.5^{c}	1.8 ± 0.5^{c}	2.5 ± 0.5^{c}	2.7 ± 0.6^{c}
Aspartate	0.3 ± 0.1^{b}	0.2 ± 0.2	0.0 ± 0.1	
D	0.3 ± 0.2	0.0 ± 0.1	0.2 ± 0.2	0.3 ± 0.3
I	0.3 ± 0.1^{c}	0.2 ± 0.2	0.0 ± 0.2	0.4 ± 0.4
Taurine	-0.1 ± 0.2	-0.3 ± 0.2	-0.3 ± 0.2	
D	-0.5 ± 0.2^{c}	-0.5 ± 0.2	-0.6 ± 0.3	0.1 ± 0.3
I	0.2 ± 0.2	-0.2 ± 0.2	-0.1 ± 0.3	-0.6 ± 0.2^{b}
Aspargine	0.4 ± 0.2^{b}	0.2 ± 0.1	0.0 ± 0.1	
D	0.5 ± 0.1^{c}	0.1 ± 0.1	-0.1 ± 0.2	0.2 ± 0.2
I	0.4 ± 0.4	0.3 ± 0.2	0.1 ± 0.2	0.3 ± 0.2

[a] All values shown as micromoles per minute. Flux value significantly different from 0: [b] $p < 0.05$; [c] $p < 0.01$. Significant difference compared with observation obtained 30 minutes earlier within group: [d] $p < 0.05$; [e] $p < 0.01$. Significant difference between groups: [f] $p < 0.05$.

Abbreviations as in Table 2.

The arterial glucose level increased from 7.1 ± 0.4 to 7.6 ± 0.4 mmol/L ($p < 0.01$) during the first infusion period, and from 8.1 ± 0.8 to 8.5 ± 0.9 mmol/L ($p < 0.01$) during the second infusion period. There was no change in glucose flux, and no uptake was observed.

The arterial lactate level was unchanged, and there was no significant uptake or release of lactate.

The arterial pyruvate level was unchanged, and there was no uptake or release of pyruvate. An inverse relationship between myocardial flux of pyruvate and myocardial oxygen consumption was observed ($r_s = -0.77$; $p < 0.05$) (Fig 1).

The arterial level of β-hydroxybutyrate increased during the first dopamine infusion from 687 ± 64 to 799 ± 80 μmol/L ($p < 0.01$). There was no change in ketone flux, and no uptake was observed.

Dopamine had no obvious effect on the arterial levels or flux of any amino acid. There was, however, a tendency toward an increased release of alanine ($p = 0.056$).

Effects of Insulin-Dopamine

HEMODYNAMIC VARIABLES (Table 2). Cardiac index increased 41.8% ± 4.7% during insulin-dopamine infusion, which was significantly greater than during dopamine infusion in the second study period (25.9% ± 6.7%; $p < 0.05$). Systemic vascular resistance decreased 27.4% ± 5.1% in the insulin-dopamine group in contrast to the

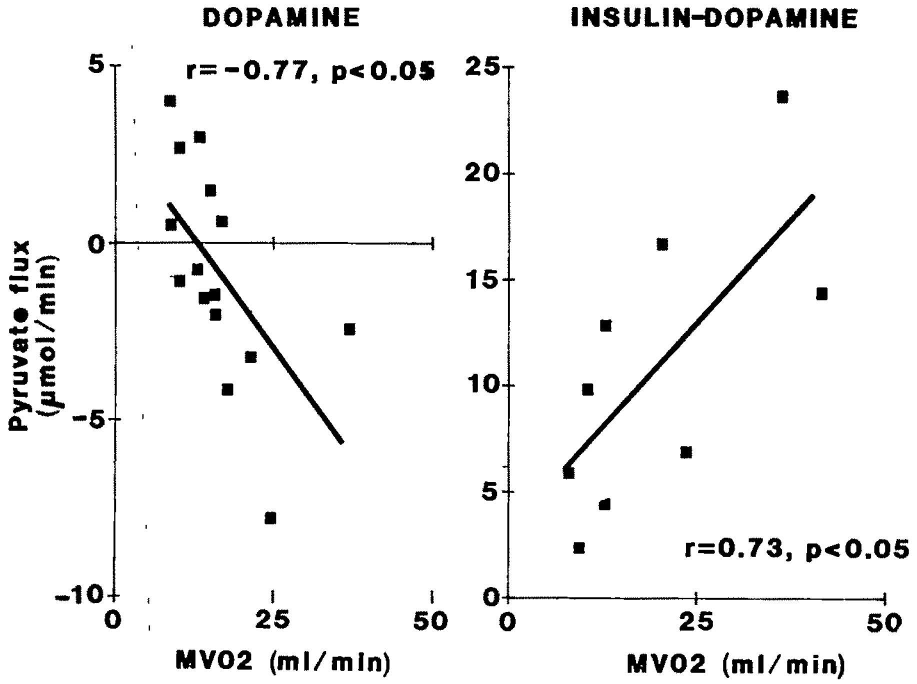

Fig 1. Relationship between myocardial oxygen uptake (MVO2) and myocardial flux of pyruvate during dopamine infusion and during combined infusion of insulin and dopamine.

dopamine group, where it was unchanged (−3.8% ± 6.7%).

MYOCARDIAL UPTAKE OF OXYGEN (Table 2). Myocardial oxygen uptake increased by 78.8% ± 18.4% while coronary sinus blood flow only increased by 35.8% ± 14.2%. Thus coronary sinus blood oxygen saturation decreased from 47.0% ± 1.7% to 31.5% ± 3.4%.

MYOCARDIAL UPTAKE OF SUBSTRATES (Tables 3, 4). The arterial levels of FFAs decreased from 795 ± 87 to 328 ± 80 µmol/L ($p < 0.01$). Arterial-coronary sinus plasma concentration differences of FFAs correlated with arterial FFA levels ($r_s = 0.72$; $p < 0.01$) (Fig 2). There was no longer a significant uptake of FFAs.

The arterial glycerol level was unaffected but the infusion of insulin-dopamine was associated with a release of glycerol (−4.9 ± 2.6 µmol/min).

The arterial glucose level was maintained by a glucose infusion (7.8 ± 0.7 mmol/L). Insulin-dopamine infusion resulted in a significant glucose uptake of 40.9 ± 21.3 µmol/min ($p < 0.01$). The arterial lactate level increased

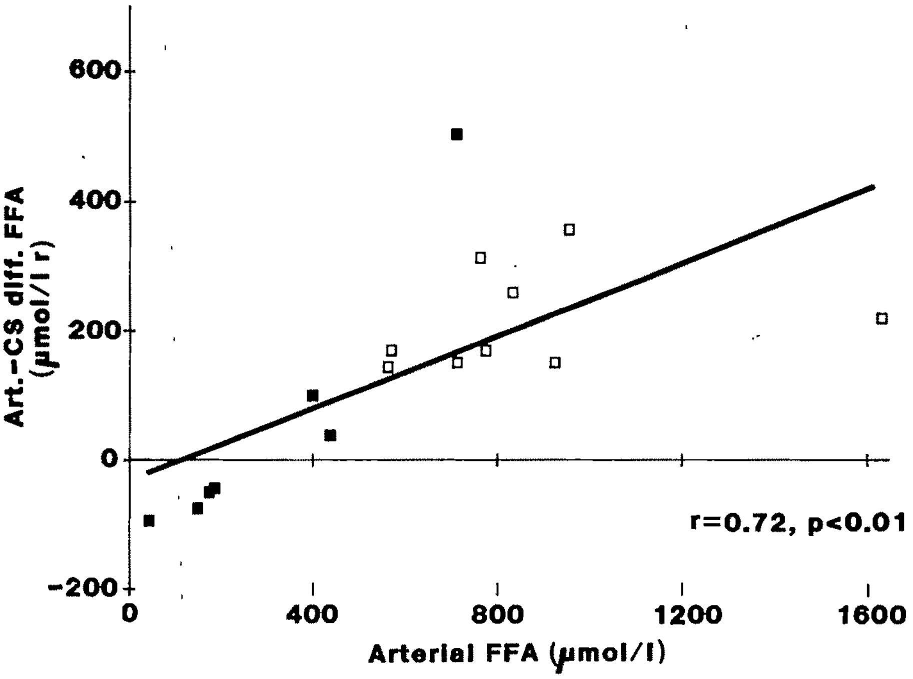

Fig 2. Relationship between arterial concentrations of free fatty acids (FFA) and arterial-coronary sinus plasma concentration differences of FFA during the second study period. Filled squares *represent insulin-dopamine patients and* open squares *represent dopamine patients.*

from 2.32 ± 0.26 to 3.56 ± 0.39 mmol/L, but no uptake of lactate was observed.

The arterial pyruvate level increased from 171 ± 17 to 302 ± 27 μmol/L ($p < 0.01$). The arterial level of pyruvate correlated with the uptake of pyruvate ($r_s = 0.67$; $p < 0.05$), and a significant uptake of pyruvate was observed (10.8 ± 2.3 μmol/min; $p < 0.01$). To evaluate the importance of the increased arterial pyruvate concentration and the insulin infusion on the increased uptake of pyruvate, a multiple regression analysis was performed. Insulin infusion could explain 77% of the variation in myocardial uptake ($r^2 = 0.77$; $p < 0.001$). Inclusion of arterial pyruvate increase during insulin infusion did not improve the model (partial correlation = 0.27; $p = 0.32$).

In contrast to the inverse relationship between oxygen consumption and pyruvate flux that was observed during dopamine infusion, a positive correlation between myocardial oxygen consumption and pyruvate uptake was observed ($r_s = 0.73$; $p < 0.05$) (Fig 1).

The arterial level of β-hydroxybutyrate decreased from 674 ± 114 to 488 ± 91 μmol/L ($p < 0.05$). There was no uptake of β-hydroxybutyrate.

The arterial levels of the branched-chain amino acids (leucine, isoleucine, valine), lysine, threonine, tyrosine, ornithine, threonine, α-aminobutyric acid, and serine decreased. Flux of most amino acids was unchanged with the exception that an uptake of arginine and change toward a more positive methionine balance occurred.

Comment

This study deals primarily with the effects of dopamine and a combination of dopamine and high-dose insulin on myocardial energy metabolism early after a cardiac operation. Infusion of dopamine increased myocardial oxygen expenditure by 60% to 70%, but no concomitant change of myocardial substrate uptake was observed. The addition of high-dose insulin to dopamine induced a marked reduction of arterial FFA level and a shift toward carbohydrate utilization at the expense of FFAs. Thus, the desired metabolic effects of insulin were obtained regardless of dopamine.

Effects of Dopamine

Dopamine was infused at a moderate dose, which was expected to exert clear inotropic, minor chronotropic, and vasoconstrictive effects [9]. Basically the anticipated effects were obtained, with a 40% increase of cardiac index, the result of equal increases of stroke volume and heart rate.

The hemodynamic effects were accompanied by systemic metabolic effects suggesting an amplified trauma response. Thus, there was a 15% rise of systemic oxygen consumption and the arterial levels of glucose, FFAs, and β-hydroxybutyrate increased, suggesting increased gluconeogenic activity and increased lipolysis, respectively.

The metabolism of the heart was also changed by dopamine, in fact more markedly than systemic metabolism. Thus, there was a 60% to 70% rise of myocardial oxygen consumption. A slight uptake of β-hydroxybutyrate, previously not detectable, was observed. In spite of elevated arterial levels of FFAs and glucose there was no increase in myocardial uptake of these substrates. One would have expected the uptake of FFAs to have increased because generally the uptake of FFAs is related to the arterial level of FFAs [1, 10] (see Fig 2). A type II error may be suspected. Even so, the marked increase of myocardial oxygen expenditure was in no way matched by changes in the uptake of substrates. Oxygen-wasting effects of FFAs at high circulating levels of catecholamines may be considered [2, 4].

The lack of effect on myocardial uptake of glucose was expected. The insulin resistance in this period is to some extent the effect of increased catecholamine activity, and the infusion of dopamine was anticipated to increase this resistance further [11, 12].

The increasing release of pyruvate associated with increased uptake of oxygen may suggest that dopamine enhanced the production of pyruvate, possibly by stimulating glycogenolysis.

Effects of Insulin-Dopamine

In previous studies we observed that insulin has hemodynamic effects per se, in addition to effects on the metabolism of the heart. To obtain hemodynamic effects, doses far exceeding those that were required for maximal metabolic effects had to be employed [5]. In the present study insulin was used in hemodynamic doses.

As was anticipated from canine experiments, the addition of high-dose insulin enhanced the hemodynamic effects of dopamine. A further improved cardiac output was obtained at the same myocardial oxygen expenditure. Analysis of hemodynamic data suggests that the action of insulin was primarily due to vasodilation. The metabolic effects of insulin, however, may have contributed to the improvement in oxygen economy.

The most prominent metabolic effects were a decrease in arterial FFA concentrations and a shift toward carbohydrate oxidation at the expense of FFAs. In fact, the uptake of FFAs ceased (see Fig 2), while a substantial uptake of glucose was induced. According to stoichiometric analysis carbohydrate uptake could theoretically have explained 35% of the concomitant myocardial uptake of oxygen.

The diverging metabolic effects of dopamine and insulin were illustrated by the marked changes in myocardial pyruvate flux. During dopamine infusion there was an inverse relationship between oxygen uptake and pyruvate uptake. Addition of high-dose insulin to dopamine converted it into a positive relationship. Thus, an increased oxygen consumption was associated with an increased uptake of pyruvate instead of a release (see Fig 1). This suggests enhanced elimination of pyruvate within the cell. Pyruvate may either be eliminated by transamination to alanine or be directed into the Krebs cycle via pyruvate dehydrogenase or pyruvate carboxylase activity. The present data argue against the former explanation because the release of alanine was not increased. On the contrary, the previous release of alanine ceased, and this together with increased uptake of pyruvate would suggest stimulated pyruvate dehydrogenase activity. This is in keeping with experimental data that demonstrate stimulation of pyruvate dehydrogenase by insulin. The pyruvate carboxylase reaction is anaplerotic, ie, it replenishes Krebs cycle intermediates by carboxylation of pyruvate to oxaloacetate, which probably is of importance for the recovery of oxidative metabolism after ischemia. The effects of insulin on pyruvate carboxylase in the heart are, however, not known [13–15]. It is suggested that one or both of these enzymes were stimulated, directing pyruvate into the Krebs cycle.

Stoichiometric analysis of the present data suggest that uptake of exogenous FFA and carbohydrate substrates covered no more than 75% of myocardial oxygen consumption. This in turn leaves some 25% to be explained. A release of glycerol was observed during insulin treatment. This could reflect degradation of myocardial lipid stores. The release of one glycerol molecule could represent oxidation of three FFA molecules. If this assumption is correct, it would explain the fuel deficit.

In nontrauma in vitro experiments insulin stimulates myocardial protein synthesis, and thus an increased uptake of amino acids might have been expected [16]. In the present study, however, insulin had no major effects on the myocardial uptake or release of amino acids. This is in accordance with observations from animal trauma experiments [17]. The lack of influence on myocardial uptake of amino acids could thus possibly be explained by the insulin resistance of trauma metabolism.

Conclusions and Clinical Implications

The present study demonstrates that dopamine, although improving the hemodynamic state of the patient, induces metabolic changes that may be unfavorable to the strained myocardium: an increased myocardial load of FFAs and a marked increase of myocardial oxygen expenditure, unmatched by changes in substrate uptake. Oxygen-wasting effects of FFAs at high circulating catecholamine levels are suggested.

Myocardial insulin resistance may to a significant extent be overcome by supraphysiological doses of insulin, even during infusion of adrenergic drugs. Addition of high-dose insulin to dopamine induced the desired metabolic effects: a shift toward carbohydrate oxidation at the expense of FFAs. This may be beneficial for the postischemic heart by supplying glucose and by reducing the oxygen-wasting effects of FFA metabolism and the toxic effects of intracellular FFA metabolites [2–4].

Addition of high-dose insulin to dopamine improved the hemodynamic state of the patients without further increasing myocardial oxygen demand. The present data cannot determine to what extent the changed substrate metabolism of the heart induced by high-dose insulin infusion explains the improved oxygen economy.

The clinical role of insulin in the treatment of postoperative left ventricular failure has not been established by the present investigation because the patients were not in need of inotropic therapy. It may be argued that the effects of high-dose insulin in combination with dopamine may be different and of no benefit to patients with postoperative severe cardiac dysfunction. A previous work employing a canine model with severe ischemic heart failure, however, provided data in agreement with the present findings [18]. Furthermore, the value of glucose-insulin-potassium treatment was supported by a recently published clinical study [19]. Gradinac and associates [19] reported improvement of left ventricular function in patients with refractory heart failure after a cardiac operation. A reduced need of adrenergic inotropic support and a trend toward reduction in mortality were observed. These results were obtained with a much lower dose of insulin than used in the present study. According to our previous experience, a lower dose does not have any hemodynamic effects per se in patients without heart failure; however, metabolic effects are obtained. Thus, it is conceivable that the results obtained by Gradinac and associates were due to metabolic effects, which may have a greater impact in the strained myocardium.

The potentially detrimental metabolic effects of adrenergic drugs suggest that insulin should be considered whenever these drugs have to be used in the treatment of postoperative heart failure. It is possible that larger doses of insulin may amplify the clinical impact of glucose-insulin-potassium treatment.

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Potential Use of Recombinant Hirudin as an Anticoagulant in a Cardiopulmonary Bypass Model

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Recombinant (r) hirudin is a potent thrombin-specific inhibitor derived from the natural hirudin of the leech (*Hirudo medicinalis*). We have studied the efficacy of r-hirudin compared with heparin in a canine model of cardiopulmonary bypass operations. Two administration regimens were used for r-hirudin: group 1, 1.0 mg/kg intracardiac bolus then intravenous bolus at 30 minutes (n = 10); and group 2, 1.0 mg/kg intracardiac bolus with 1.25 ± 0.04 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} intravenous infusion (n = 8). Group 3 was given an intracardiac bolus of heparin, 1.66 mg/kg (n = 9). Aspiration of blood from the chest cavity revealed no significant difference between the three groups. Measurement of fibrin deposits in the pump line filter revealed higher amounts in the r-hirudin groups (p = 0.02). Decreases in platelets, fibrinogen, and hematocrit due primarily to hemodilution were the same in each group. The bleeding time assay showed less prolongation for r-hirudin than for heparin ($p < 0.001$). No antagonist for r-hirudin was used; however, due to its short half-life all coagulation variables returned to baseline within 30 minutes after cardiopulmonary bypass. Because r-hirudin lacks effect on platelets, is a poor immunogen, does not require a plasma cofactor, and may not require an antagonist, it may provide an alternative anticoagulant to heparin in cardiopulmonary bypass. Additional studies are, however, needed to optimize the dose and to evaluate other clinical aspects of r-hirudin.

(Ann Thorac Surg 1991;51:271–7)

Heparin, the commonly employed anticoagulant for cardiopulmonary bypass (CPB) devices, may cause thrombocytopenia, arterial thrombosis, and severe bleeding in patients who have immune-mediated heparin-induced thrombocytopenia. In others there may be a deficiency of antithrombin III rendering heparin ineffective. An alternative anticoagulant for use in such patients is thus needed.

The leech has been used for hundreds of years as a medicinal, and natural hirudin extracted from the leech has been employed as a laboratory reagent for the past 100 years. However, due to the unpredictable nature of the leech and the limited supplies of purified hirudin, this anticoagulant has not become more widely used clinically. We now have sufficient supplies of purified recombinant hirudin (r-hirudin), made possible through recombinant technology, to begin animal and human studies to determine the efficacy and safety of this agent as an anticoagulant.

Although both r-hirudin and heparin are proven anticoagulants in animal models [1–6], there are several distinct differences between the two agents (Table 1). Recombinant hirudin is a thrombin-specific inhibitor [7], composed of 65 amino acids [8]. The original hirudin was obtained from the leech (*Hirudo medicinalis*). In contrast to heparin, r-hirudin is a homogeneous preparation with only one known activity. Recombinant hirudin acts by directly and tightly inhibiting thrombin without need of a cofactor, in contrast to heparin, which requires antithrombin III [9, 10]. On a gravimetric basis, r-hirudin is threefold to fivefold more potent than heparin as an anticoagulant as determined by the activated partial thromboplastin time and chromogenic anti-IIa assays [10]. Studies to date show minimal interaction of r-hirudin with platelets [11, 12]. It is not inhibited by platelet factor 4 [13]. The half-life of r-hirudin is shorter than that of heparin [14], and there appears to be a lesser bleeding potential [10, 15]. To date no immunogenicity problems have been detected with hirudin [16].

In view of the potent anticoagulant activity of r-hirudin, the comparative differences between this agent and heparin, and the relative advantages of r-hirudin, we chose to evaluate the efficacy of r-hirudin as an anticoagulant in cardiac bypass operations.

Material and Methods

Thirty male mongrel dogs with a mean weight of 28 kg underwent CPB for 1 hour. The animals were divided into three groups based on anticoagulation treatment during CPB. Group 1 was administered r-DNA-hirudin (HBW 023; Hoechst, Frankfurt, Germany) at 1.0 mg/kg by intracardiac bolus injection immediately before the pump was started and a second intravenous bolus of 1.0 mg/kg at 30 minutes of pump time. No antagonist was given at the end of pump time. Group 2 was administered r-DNA-

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Table 1. Comparison of Recombinant Hirudin and Heparin as Anticoagulant Agents

Recombinant Hirudin	Heparin
Singular molecular composition	Polycomponent molecular structures
One activity; 3- to 5-fold more potent thrombin inhibitor than heparin	Multiple activities
Limited platelet and endothelium interactions	Inhibits platelet activity and induces endothelial activity
Independent of cofactors	Dependent on AT III for expressing activity
Half-life 50 minutes (iv)	Half-life 90 minutes (iv)
Minor bleeding effects	Major bleeding effects
Not affected by platelet factor 4	Inhibited by platelet factor 4
No effect on fibrinolysis	Stimulates fibrinolysis
May not require neutralizing after CPB	Requires protamine for neutralization after CPB
Appears not to be an immune stimulant	Can produce allergic reactions

AT III = antithrombin III; CPB = cardiopulmonary bypass; iv = intravenous.

hirudin at 1.0 mg/kg by intracardiac bolus injection immediately before the pump was started followed immediately by a constant infusion of 1.25 ± 0.04 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} for the 60-minute pump time. No antagonist was given. Group 3 (control) was administered porcine mucosal heparin at 1.66 mg/kg (250 U/kg) by intracardiac bolus injection into the right atrial space immediately before the pump was started. At 60 minutes 1.66 mg/kg intravenous slow bolus of protamine sulfate was administered.

For these initial studies a 1.0 mg/kg r-hirudin dose ($\approx$15 μg/mL) was chosen. This was based on the fact that this dose should give approximately the same anticoagulant response as about 3 mg/kg ($\approx$40 μg/mL; $\approx$5 U/mL) heparin, the usual clinical dose used at our institution.

The choice of the heparin dose (1.66 mg/kg) was based on pilot studies in the same canine CPB model. This dose was found to be the lowest dose that would eliminate serious fibrin deposits in the pump line filter. This minimum effective dose would be the safest dose that would yet make it possible to obtain more useful information from the study than if an "overdose" was used. The fact that this dose is lower than that used clinically is due to the differences between human and canine physiology as well as to the lesser degree of surgical manipulation in the canine model compared with a clinical surgical situation. Nevertheless, as both r-hirudin and heparin were evaluated in the same model and by the same surgical team, a useful comparison can be made.

Dogs were anesthetized with pentobarbitol and ventilated to 3 cm H_2O positive peak end-expiratory pressure. Vascular access lines were established in the left femoral vein and artery. A drip injection of lactated Ringer's solution was established. After midsternal thoracotomy, the heart was suspended in a pericardial cradle. Cardiopulmonary bypass was established with cannulation through the right atrial appendage and ascending aorta (70 mL $\cdot$ kg^{-1} $\cdot$ min^{-1} flow, 38°C, 55 to 70-mm Hg mean arterial pressure). Cardiopulmonary bypass using a Travenol pump (Travenol Labs, Inc, Ann Arbor, MI) primed with 1 L lactated Ringer's solution and a variable-prime Cobe membrane lung blood oxygenator (Cobe, Lakewood, CO) with sterile, surgical grade Tygon S-50-HL tubing and #EC-3840 sterile Pall 40-μm blood filters was continued for 60 minutes followed by a 150-minute observation period. One surgeon was used for all experiments; no change in the operating technique was made throughout this study.

Periodically throughout the procedure arterial blood gases were measured to ensure proper ventilation of the dog. Venous blood samples were periodically collected for immediate analysis of hematocrit, platelet count, fibrinogen (Clauss technique; Dade, Miami, FL), and celite activated clotting time (ACT) (Hemochron; International Technidyne, Edison, NJ). Canine pooled plasma (normal = 3 g/L fibrinogen) was used to construct a calibration curve for the fibrinogen assay. The bleeding time test (Simplate; Organon Teknika, Durham, NC) was performed on the gingiva of the dogs.

Plasma aliquots were also kept at 4°C until frozen (−70°C) for analysis on the following day. Coagulation testing on these samples included the following assays: prothrombin time (Dade) to evaluate the extrinsic coagulation pathway; activated partial thromboplastin time (Dade) to evaluate the intrinsic coagulation pathway; 10 U/mL thrombin time (human thrombin; Ortho, Raritan, NJ) to evaluate the thrombin-fibrinogen interaction; 10 U/mL calcium-thrombin time (using thrombin time reagents reconstituted in 0.025M $CaCl_2$ not saline solution), a modification of the thrombin time assay; Heptest and Heptest-Hi (Haemachem, Inc, St. Louis, MO), an activated partial thromboplastin time–like assay of greater sensitivity to anticoagulant effects; and a chromogenic substrate anti-factor IIa kinetic rate assay [17] specific for measuring the inhibition of thrombin in plasma. All clotting assays were performed on Fibrometers. The chromogenic assay was performed on a Beckman kinetic recording spectrophotometer.

Pump line filters were collected, washed with 1.0 L saline solution, and dried by forced air for 10 minutes immediately after the dog was removed from the pump. Fibrin deposits in the pump filters were measured by the Folin-Ciocalteu phenol fibrinogen/protein assay as previously described [18]. Blood loss was measured by weight of aspirated blood collected from the chest cavity after the pump period and after the observation period. All dogs were killed with supersaturated potassium chloride after the observation period. The abdominal cavity was explored for bleeding and clotting. Tissue samples of liver, lung, heart, and kidney were collected and preserved in formalin for histological examination for microthrombi.

These studies were conducted in the Animal Research

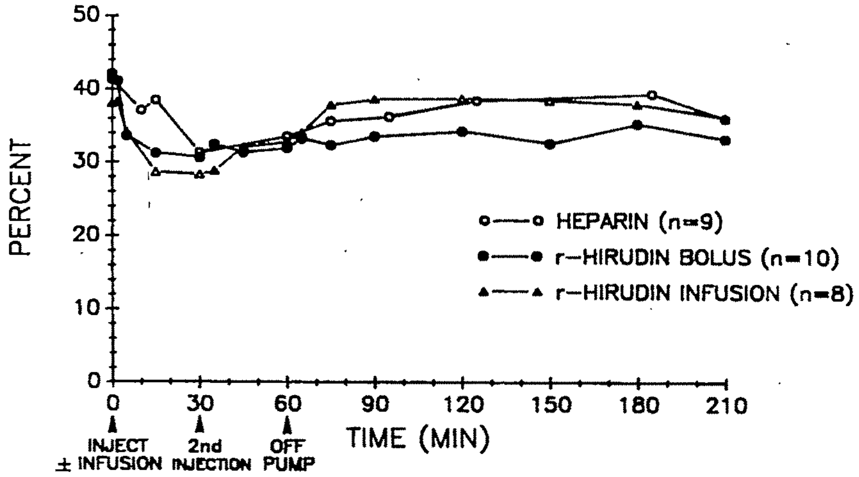


Fig 1. Effect of r-hirudin (2 × 1.0 mg/kg bolus or 1.0 mg/kg bolus with 1.25 mg · kg^{-1} · h^{-1} infusion) and heparin (1.66 mg/kg bolus) treatment on the hematocrit of dogs during a cardiopulmonary bypass operation. Hematocrit (%) was measured before and throughout the 60-minute pump time and during the 150-minute follow-up period. Results are given as a mean.

Facilities of Hines VA Hospital (Hines, IL), which is accredited by the American Association for the Accreditation of Laboratory Animal Care.

Results

Hematocrit showed an initial decrease of not more than 0.13 (a 30% decrease from the initial hematocrit value) due to hemodilution with no further decrease during CPB for the two r-hirudin and heparin dosing regimens (Fig 1; standard errors of the mean were not included on the graphs for ease of interpretation). Platelet count (Fig 2) and fibrinogen similarly responded with a decrease due to hemodilution but no further decrease. Platelet values remained in the normal range throughout the experimental period. Fibrinogen levels decreased from 3.25 to 1.70 g/L. Although variations were observed between dogs, overall no significant differences were observed between the r-hirudin and heparin groups for these three variables over the experimental period ($p > 0.010$, Newman-Keuls one-way analysis of variance [ANOVA]).

Total blood loss for the duration of the procedure was 452 ± 133, 361 ± 35, and 382 ± 47 g for groups 1, 2, and 3, respectively (Table 2, Fig 3). There was no significant difference between the two drug regimens of r-hirudin and heparin for total blood loss aspirated from the chest cavity. If evaluated with respect to time, after the 60-minute pump time, there was slightly more bleeding in both r-hirudin groups as compared with the heparin group; however, this difference was not significant ($p = 0.090$, repeated-measures ANOVA). During the 150-minute observation period after the pump period, there was no significant difference in blood loss between the three groups ($p > 0.10$, repeated-measures ANOVA).

No clots were observed in the CPB circuitry for any dog. Pump line filters analyzed for fibrin deposits showed similar results in the two r-hirudin groups. The amount of fibrin deposit in the r-hirudin treatment groups was significantly higher than that observed in the heparin group (see Table 2) ($p = 0.020$, repeated-measures ANOVA).

The bleeding time test showed 9:02 ± 1:40 (minutes: seconds), 6:28 ± 2:10, and greater than 15 minutes for groups 1, 2, and 3, respectively, during CPB (Fig 4). The baseline (before anticoagulation) bleeding time values of all dogs were not significantly different ($p > 0.10$, repeated-measures ANOVA). After the initial intracardiac injection, the two r-hirudin groups showed moderately ele-

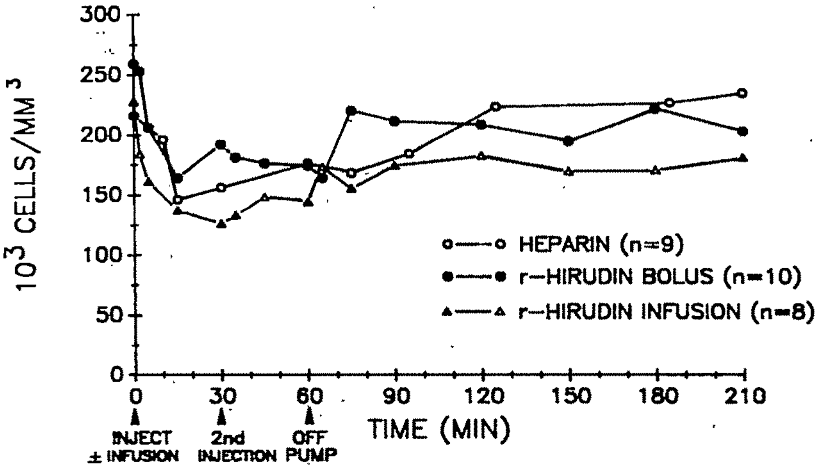


Fig 2. Effect of r-hirudin (2 × 1.0 mg/kg bolus or 1.0 mg/kg bolus with 1.25 mg · kg^{-1} · h^{-1} infusion) and heparin (1.66 mg/kg bolus) treatment on the platelet count of dogs during a cardiopulmonary bypass operation. Platelets were measured before and throughout the 60-minute pump time and during the 150-minute follow-up period. Results are given as a mean.

Table 2. Comparative Efficacy of Recombinant Hirudin and Heparin in a Canine Cardiopulmonary Bypass Model[a]

Group	Chest Cavity Blood Loss (g)	Clots in Pump Line Filters (mg)
1: r-Hirudin Bolus (n = 10)		
After Pump	201 ± 49	126 ± 37[b]
After 150 minutes	251 ± 84	
Total	452 ± 67	
2: r-Hirudin Infusion (n = 8)		
After Pump	134 ± 27	208 ± 50[b]
After 150 minutes	227 ± 42	
Total	361 ± 35	
3: Heparin (n = 9)		
After Pump	259 ± 54	22 ± 3
After 150 minutes	123 ± 39	
Total	382 ± 47	

[a] Dogs were maintained on CPB for 1 hour under one of three drug regimens (r-hirudin at 2 × 1.0 mg/kg bolus; or 1.0 mg/kg bolus with 1.25 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion; or heparin at 1.66 mg/kg bolus). After CPB, pump line filters were analyzed for amount of fibrin deposit. Blood loss was collected from dog chest cavities by aspiration after the pump period and after the 150-minute observation period that followed the pump period. [b] $p = 0.02$ compared with group 3.

CPB = cardiopulmonary bypass; r-hirudin = recombinant hirudin.

vated bleeding time values (normal, 2.56 ± 0.25 minutes), which remained constant throughout CPB. There was a slight difference in bleeding time values between the two r-hirudin groups. This is due to the difference in the pharmacokinetic response, in particular the rapid elimination rate, of the two bolus injections as compared with the infusion. This can be referenced against the time at which the test was performed.

Conversely, the bleeding time in the heparin group did not reach an endpoint when measured at 30 minutes of CPB. The difference in bleeding time values between either r-hirudin group and the heparin group at 30 minutes of pump time was significantly different ($p < 0.001$, repeated-measures ANOVA).

Of the several different clot-based coagulation tests performed on the blood of these dogs none, including the ACT, gave acceptable readings during CPB for both r-hirudin and heparin. Assay values during time of full anticoagulation were beyond the sensitivity limits of each assay.

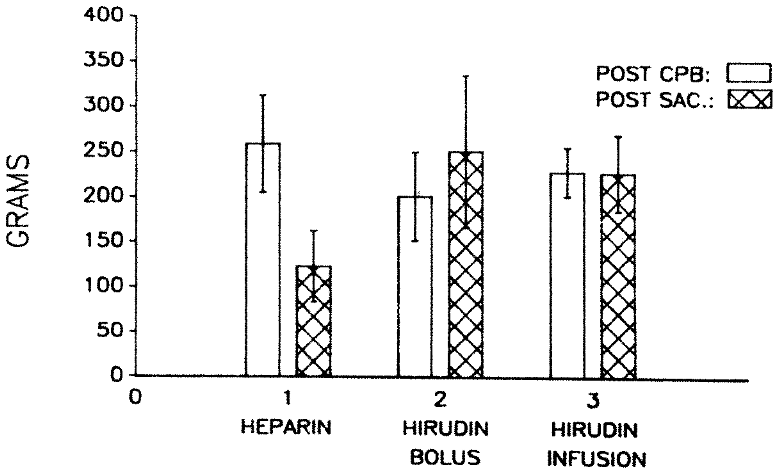
All coagulation assays except the thrombin time assay, which remained elevated, were able to detect the elimination rate of r-hirudin and heparin after CPB. Baseline levels were reached within 30 minutes after the pump period for both r-hirudin groups. The heparin group reached baseline values for the above assays immediately after the injection of protamine sulfate.

The ACT data for the three groups are shown in Figure 5. Off-scale values were obtained for the anticoagulation response by both r-hirudin bolus and heparin. Owing to the difference in the pharmacokinetics of r-hirudin when given by the two administration regimens, a different pattern of absorption and elimination as evidenced by the ACT response was observed. The highly sensitive ACT response to heparinized blood, which is not observed to such a degree in humans, is most likely owing to the difference between dog and human blood coagulation systems.

The only assay that gave measurable endpoints in the r-hirudin group during CPB was a modification (1:10 dilution of plasma) of the chromogenic anti-factor IIa assay, which was originally developed for monitoring heparin activity (Fig 6). This assay measures only the inhibitory effect of a drug on factor IIa (thrombin). The drawback, however, is the slow turnaround time of this plasma-based assay compared with the ACT. The blood from the heparin-treated dogs was evaluated by the original (no plasma dilution) method.

In general more consistent anticoagulant responses were obtained with the infusion regimen of r-hirudin than with the bolus regimen. Dogs remained fully anticoagulated throughout the entire pump time with the infusion. The bolus r-hirudin showed loss of anticoagulant activity within 30 minutes after administration of the agent, which

Fig 3. Comparison of chest cavity blood loss in r-hirudin (2 × 1.0 mg/kg bolus or 1.0 mg/kg bolus with 1.25 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion) and heparin (1.66 mg/kg bolus) treated dogs during a cardiopulmonary bypass operation. Blood loss in the chest cavity (grams of aspirated material) was measured for the 60-minute pump time (CPB) and during the 150-minute observation period after the pump time (SAC). Results are given as a mean ± standard error of the mean.



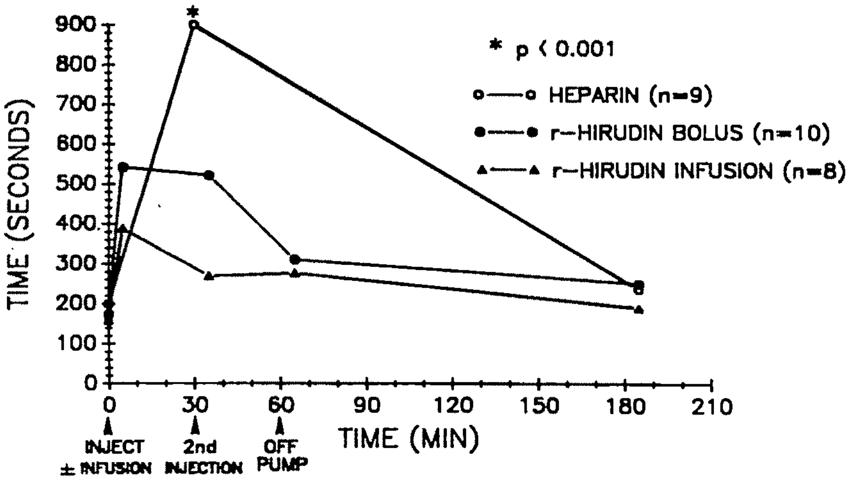


Fig 4. Comparison of the bleeding time assay in r-hirudin (2 × 1.0 mg/kg bolus or 1.0 mg/kg bolus with 1.25 mg · kg^{-1} · h^{-1} infusion) and heparin (1.66 mg/kg bolus) treated dogs during a cardiopulmonary bypass operation. Bleeding time (Simplate device) was measured before and once or twice during the 60-minute pump time and at the end of the 150-minute observation period. Results are given as a mean. At 30 minutes' pump time the heparin treatment showed a highly significant increase in bleeding time compared with both r-hirudin–treated groups.

was regained upon the second injection. Owing to the longer half-life of heparin, the dogs in this group remained fully anticoagulated for the 60-minute pump time with only one intracardiac injection.

The histological examination of the major organs revealed no observable differences between dogs receiving r-hirudin and heparin. No microthrombi that could be attributed to a lack of anticoagulation were detected in the sections of lung, liver, heart, or kidney studied. Examination of the abdominal cavity for excess bleeding or clotting after CPB did not reveal any significant findings in any of the three groups.

Comment

Several previous studies have investigated the use of alternate anticoagulants in cardiac surgery using extracorporeal circulation. The newly developed low-molecular-weight heparins [19, 20] and certain heparinoids (21) have been studied in preliminary protocols with variable success. In our investigation, we have taken a somewhat different approach and chosen an anticoagulant that is very potent, yet working via a different mechanism of action than heparin and heparin-related agents. This difference should afford a better clinical outcome to patients sensitive to heparin than might be gained by the heparin-related agents.

Using r-hirudin as an anticoagulant in a CPB surgical model, the extracorporeal circuit remained patent for a 1-hour pump time under the dosing regimens studied. There was no evidence of vascular occlusion or hemorrhage in any of the vital organs, and there were no obvious adverse reactions of the dogs to r-hirudin in terms of cardiac or respiratory function. Platelets and fibrinogen remained in the normal range throughout the experimental period. None of the dogs died prematurely from excessive bleeding, clotting, or apparent drug-related reaction.

During the procedure it was impossible to distinguish heparin treatment from r-hirudin treatment other than by the bleeding time test, which was much less affected by r-hirudin than by heparin. Interestingly, the bleeding time response was only moderately elevated in both r-hirudin groups but excessively prolonged in the heparin

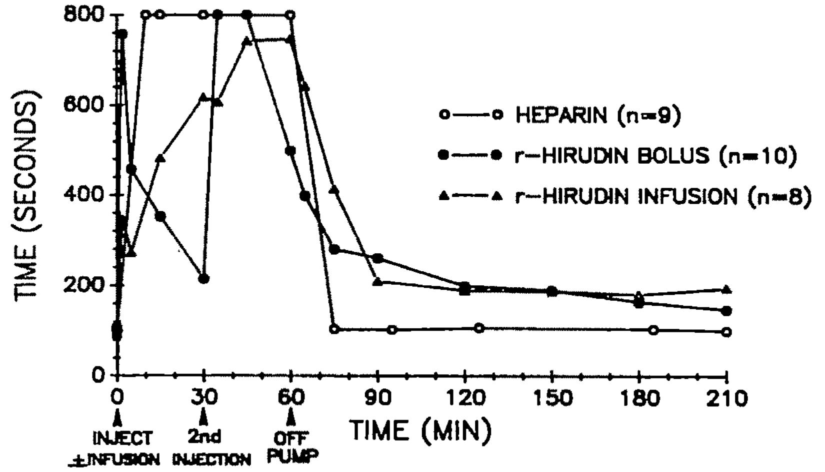
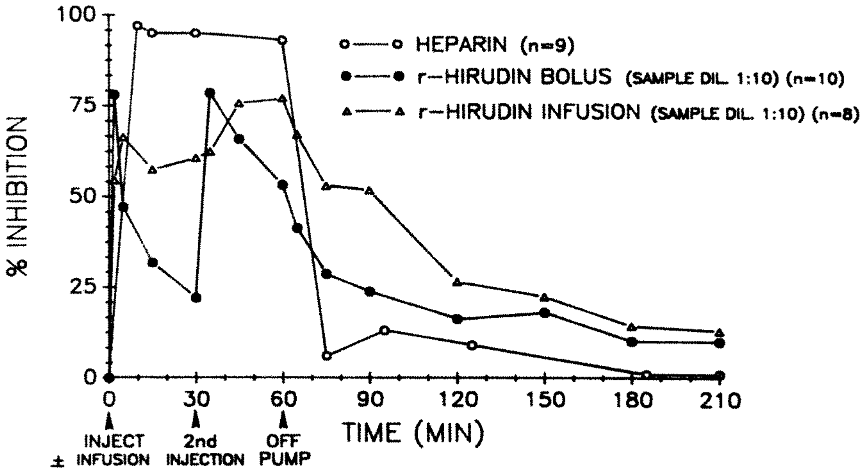


Fig 5. Effect of r-hirudin (2 × 1.0 mg/kg bolus or 1.0 mg/kg bolus with 1.25 mg · kg^{-1} · h^{-1} infusion) and heparin (1.66 mg/kg bolus) treatment on the celite activated clotting time in dogs during a cardiopulmonary bypass operation. Activated clotting time was measured before and throughout the 60-minute pump time and during the 150-minute follow-up period. Results are given as a mean.

Fig 6. Effect of r-hirudin (2 × 1.0 mg/kg bolus or 1.0 mg/kg bolus with 1.25 mg · kg^{-1} · h^{-1} infusion) and heparin (1.66 mg/kg bolus) treatment on the anti-factor IIa assay in dogs during a cardiopulmonary bypass operation. Anti-factor IIa assay (% inhibition of thrombin) was measured before and throughout the 60-minute pump time and during the 150-minute follow-up period. Results are given as a mean. Plasma samples from r-hirudin-treated dogs were diluted 1:10 in buffer before assaying.



group. The bleeding time test is dependent on coagulation, platelet, and endothelial function. Because the coagulation system is strongly inhibited by both r-hirudin and heparin, it can be speculated that the lesser effect on the bleeding time test by r-hirudin than by heparin may be due to its lesser inhibition of platelet aggregation [12].

The appearance of more fibrin deposits in the pump line filters in the two r-hirudin groups, as compared with the heparin group, suggests that a higher dose is needed. Because blood loss in the chest cavity was equal to that of heparin, and the bleeding time test was less affected, an increase in the dose of r-hirudin should provide more effective anticoagulation without substantially increasing blood loss.

The infusion of r-hirudin gave a more consistent anticoagulation response than the bolus regimen. Although the efficacy and safety of r-hirudin as measured by blood loss, filter fibrin deposits, and bleeding time of r-hirudin were not significantly different between the two regimens in this study, an infusion of r-hirudin would provide for more stability in the procedure. In our experience there were individual responses to anticoagulation by r-hirudin, as is observed with heparin. At the same dosage based on body weight certain dogs responded either more or less strongly to the anticoagulation as judged by their blood tests. Therefore, it would be best to have a means to monitor an individual's response to r-hirudin to be able to give an adjusted dose for a given anticoagulation level and not to give a fixed dose to all patients.

In this study, monitoring of the anticoagulation response during CPB did not give measurable readings by the routine whole blood or plasma-based clotting assays. To monitor the level of anticoagulation during CPB with r-hirudin, new or modified assays of a practical nature for the operating room setting may be required. It should be remembered, however, that the canine physiology and hemostatic system differ from those of the human, and also that dogs respond differently to anticoagulation than humans. Thus the dosing used in the dogs and the blood test responses obtained are not directly transferable to the human situation.

One of the most intriguing observations in this study was the natural return to baseline of all clotting assays and bleeding time tests in the r-hirudin-treated animals within 30 minutes after the pump period. It is known that the half-life of intravenously administered r-hirudin is about 50 minutes in normal dogs and that this agent is cleared about 95% through the kidney in dogs [14]. Thus, in patients with normal kidney function, there may be no need for neutralization by drug intervention.

At this time, there is no known antagonist to r-hirudin. Several studies have been done, however, that show a partial reversal of the bleeding effect of r-hirudin by factor VIIa concentrates or prothrombin complex concentrates [10]. Suggestions for other antagonists include antibodies to r-hirudin, fresh frozen plasma, and enzymes.

The data shown herein describe the initial investigation for the potential use of r-hirudin in CPB. In summary, the outcome of the study showed that r-hirudin can be used as an anticoagulant during CPB operations, although the efficacy at the dosage studied was not as optimal as with heparin. Nevertheless, these data are strong enough to warrant further studies of r-hirudin in CPB to determine a more optimum dose and mode of administration. The data support the impression that a higher dose would be as efficacious as heparin without inducing any more bleeding than occurs with heparin therapy. If this should be the case, we will have found a much-needed substitute for heparin as an anticoagulant in CPB for those patients who cannot tolerate heparin. Ultimately it may also be shown that there is less postoperative bleeding, but our data do not support this at this time. Further studies are also needed to determine the best monitoring assay and to find an effective antagonist. It will be important to determine the interaction of r-hirudin with other drugs, particularly with antiplatelet agents. Previous studies have shown that immunogenicity of r-hirudin is low in humans, but this should be confirmed by continuing studies.

Because r-hirudin has been shown to be an effective antithrombotic agent in animal models of disseminated intravascular coagulation [22], arterial thrombosis [23], coronary thrombosis [24], and now for cardiac operations with extracorporeal circulation in a canine model, we feel it could eventually prove to be a useful substitute for heparin in humans.

We are sincerely grateful to Michael Koza, BS, MT (ASCP), and Michael Wallock, CCP, for their indispensable expertise and dedication in performing these experimental studies, and further to M. Koza for data analysis and statistical evaluation.

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Optimizing Myocardial Hypothermia: I. Temperature Probe Design and Clinical Inferences

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Myocardial hypothermia is an essential component of myocardial preservation for most cardiac operations. Because of multiple causes of rewarming, it is necessary to monitor temperatures at specific sites (right and left ventricular epicardium and endocardium or cavity). Thus, plastic temperature probes have been designed and fabricated to facilitate temperature monitoring at these sites. Using a bare thermocouple as a standard, in vitro comparison of metallic probes and plastic probes revealed differences of 4.0° ± 0.9°C and 0.7° ± 0.6°C, respectively ($p < 0.005$). Consequently, metallic probes do not have sufficient accuracy to detect transmural temperature gradients because of "stem effect." Using the plastic probes to evaluate temperature changes in porcine hearts after cardioplegia-induced hypothermia revealed a temperature rise of 1°C/min at all sites if control of systemic and venous return and local myocardial cooling are not provided. The use of temperature monitoring at multiple sites permits identification and prevention of various causes of myocardial rewarming and is facilitated by the use of plastic probes described herein which contain dual thermocouples.

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Hypothermic cardioplegia and local myocardial hypothermia are frequently used for clinical myocardial protection [1–3]. Although the relative contributions of each to myocardial preservation have been debated [4–6], there is general agreement that myocardial hypothermia to 15°C or, preferably, less is desired [5, 6] and is an essential component of myocardial protection [7–9].

Various methods of maintenance of myocardial hypothermia, after induction by hypothermic cardioplegia, have been described [10–13]. However, inconsistent results with respect to maintenance of myocardial hypothermia have been reported [14–16]. Additionally, sources of rewarming have been identified [17] and quantitated [18–20].

To further evaluate and quantitate myocardial heat gain and loss, we have developed temperature probes specifically for this purpose. These temperature probes are described, validated experimentally, and used to define myocardial temperature changes in 12 pigs during induced cardiac hypothermia.

Material and Methods

Probe Design

The temperature probes are made of a pliant plastic that is molded into the approximate shape of a thumbtack with a head and needle (Fig 1). The heads of the probes are rounded with the wires exiting parallel to the cardiac surface. The plastic needles are approximately 1 mm in diameter, are of three different lengths (8 mm for the right ventricular epicardium [RVE] and myocardium or cavity [RVM], 16 mm for the left ventricular epicardium [LVE] and myocardium or cavity [LVM], and 30 mm for the interventricular septum), and are beveled to a point at the distal end. Thermocouples are used as the temperature sensing elements in all probes. All three probes have a thermocouple located within 1.0 mm of the distal tip of the needle to document either the deeper myocardial, cavity, or septal temperatures. In addition, the right ventricular (RV) and left ventricular (LV) probes have thermocouples located near the head of the probe to measure epicardial temperatures. Because the epicardial and myocardial sensors are separated by a fixed distance in a given probe (RV, 6 mm; LV, 14 mm), transmural temperature gradients can be computed by dividing the temperature difference by the corresponding distance. The system accuracy is approximately ± 0.1°C and the time constant is about 1.5 seconds and 10 seconds for the endocardial and epicardial temperatures, respectively. In use, the probes are advanced into avascular regions at their respective sites (RV anterior wall, LV inferior wall, septum near the apex) (Fig 2), connected to temperature readouts, and left in place throughout myocardial ischemia providing continuous reading at all temperature sites (see Comment section).

Temperature Probe Stem Effects Experiments

IN VITRO COMPARISON WITH METALLIC PROBES. Two sets of experiments were performed to measure the accuracy of plastic and metal temperature probes when transmural temperature gradients exist. The first set of experiments involved in vitro measurements (Fig 3). A 2-cm-thick slab of beef heart muscle was placed on top of a hot plate initially at room temperature (24°C). The beef heart slab was topically cooled on its upper surface (0°C) while the hot plate was heated from 24° to 37°C. Two simultaneous

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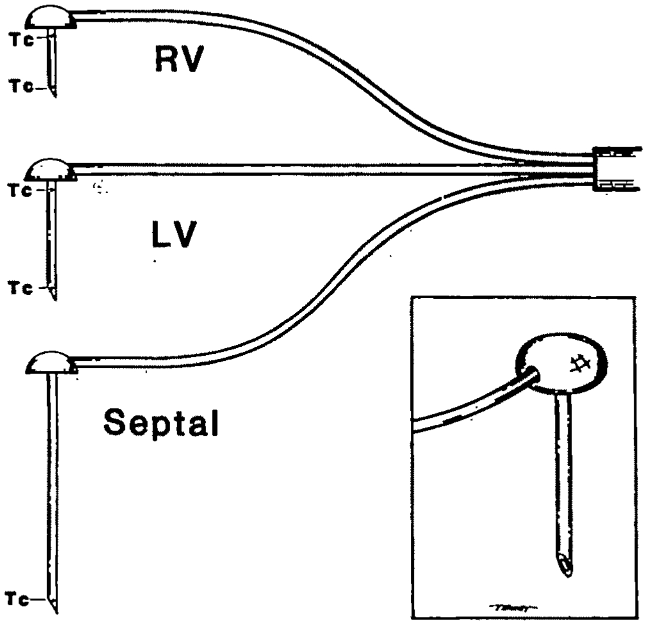

Fig 1. Temperature probe design: thermocouples (Tc) are located at the hubs and tips of the right ventricular (RV) and left ventricular (LV) probes. The septal probe contains a thermocouple only at the tip.

sets of temperature measurements were made, all at a depth of 10 mm. The first set compared a bare implanted thermocouple versus a plastic myocardial temperature probe in close proximity. The second set compared another implanted thermocouple versus a metal needle (Shiley Disposable Myocardial Temperature Probes, Model DPM; Shiley, Inc, Irvine, CA). Both needles were 1 mm in diameter and 10 mm long and used the same type of thermocouples. Temperatures were continuously recorded.

The data were analyzed by computing the average temperature differences between the bare thermocouple and the metal or plastic temperature probes over the range of 0° to 37°C.

TEMPERATURE CHANGES. Twelve immature pigs weighing approximately 25 kg were anesthetized initially with fentanyl. Anesthesia was maintained with morphine and halothane. The pigs were intubated and mechanically ventilated. Exposure of the heart was obtained by median sternotomy and pericardiotomy. The temperature probes were placed as previously described (see Fig 2) except that an RVE thermocouple was not used. All temperatures were recorded continuously on a strip chart recorder. After heparinization, the ascending aorta was cannulated and transatrial bicaval cannulation *without* caval snares was performed. Bypass was established and a systemic temperature of 28°C was obtained. With the probes in place, the aorta was cross-clamped and cardioplegia solution at 6°C was infused at 80 to 100 mm Hg pressure in the aortic root until myocardial cooling reached an equilibrium value. Temperatures recorded at this time were designated T_0. No topical cooling techniques were used. Ten minutes after cardioplegia infusion, recorded temperatures were designated T_{10}.

The data were analyzed in the following manner. The T_0 and T_{10} data for each of the four temperature recording sites were subjected to a two-way analysis of variance [21]. A significant interaction between site and time would indicate different temperatures in the sites at the two times. When a significant interaction was achieved, individual comparisons were made between RVE and LVE temperatures and LVE and LVM temperatures at T_0 or T_{10} based on Tukey's [22] method, which corrects for multiple comparisons. In addition, average rewarming rates for all sites were computed and compared using a paired *t* test.

Results

In Vitro Comparison of Plastic and Metallic Probe With Bare Thermocouple Temperature Probe Stem Effect

The average temperature difference between each probe and the bare thermocouple with the hot plate between 0°C and 37°C (temperature gradient of 1.35° to 1.85°C/mm) was 0.7° ± 0.6°C for the plastic probe and 4.0° ± 0.9°C for the metal probe (*t* test, $p < 0.005$). When normalized for

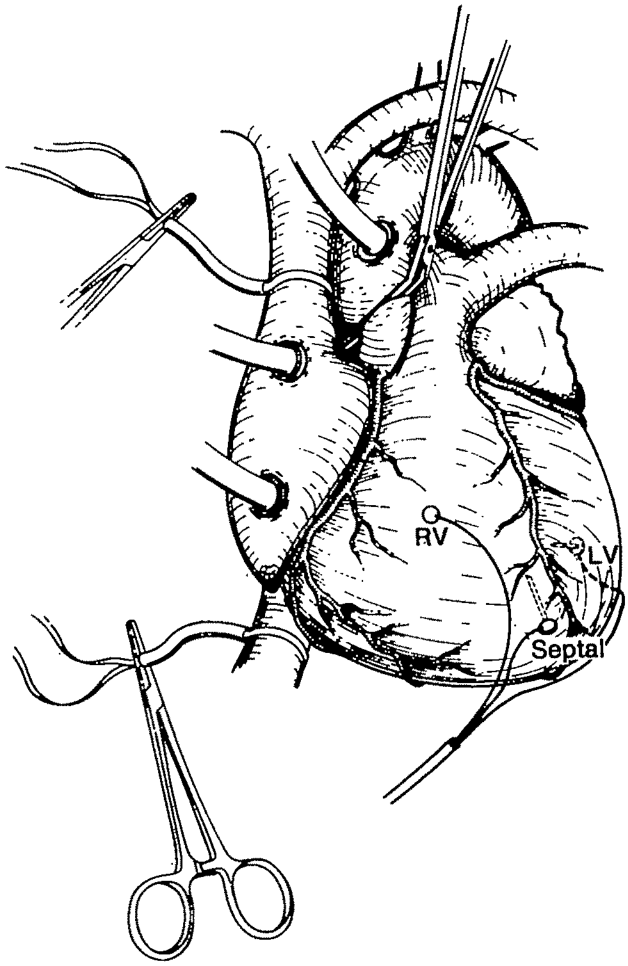

Fig 2. Temperature probe locations: the right ventricular (RV) probe is placed anteriorly, whereas the left ventricular (LV) probe is placed posteriorly. The septal probe is introduced at the apex.

the temperature gradient, the temperature differences for the plastic and metal probes averaged $0.4°C \cdot °C^{-1} \cdot mm^{-1}$ and $2.5°C \cdot °C^{-1} \cdot mm^{-1}$, respectively (relative to the bare thermocouple).

Temperature Changes in Pig Hearts

The results of the acute swine model are summarized in Table 1. Upon infusion of the cold cardioplegia solution, cardiac temperatures generally fell to equilibrium values within 3 to 4 minutes. A significant interaction between site and temperature was detected by the analysis of variance. The LVM and interventricular septum reached lower temperatures while the LVE and RVM were slightly warmer. At T_0, the RVM averaged 2.4° ± 2.9°C warmer than the LVM (Tukey's test, $p < 0.01$); the range of differences (RVM − LVM) was 9° to −2°C. Thus the RV myocardium-endocardium was more difficult to cool than the LVM.

The average LV transmural temperature difference after cardioplegia was 1.7° ± 2.1°C (epicardial > endocardial) (paired t test, $p < 0.005$); the range of differences (epicardial − endocardial) was 6° to −2°C. Thus, immediately after cardioplegia, the direction of heat flow was from epicardium to endocardium (rewarming). Because these temperature differences were recorded across a distance of 10 mm, the average transmural temperature gradient was 1.7°C/cm.

Spontaneous rewarming occurred at all sites immediately after infusion of cardioplegia was stopped. Over a 10-minute period, the various regions rewarmed at approximately 1°C/minute (see Table 1). At T_{10} the values obtained for the above comparisons were not significantly different by analysis of variance. The LVE temperature was still greater than the endocardial temperature, but only by an average of 0.4° ± 2.5°C (not significant) and the range (epicardial − endocardial) was 5° to −3°C. In contrast to the situation at T_0, the RV endocardial temperature was 1.8° ± 4.3°C less than the LV endocardium (not significant).

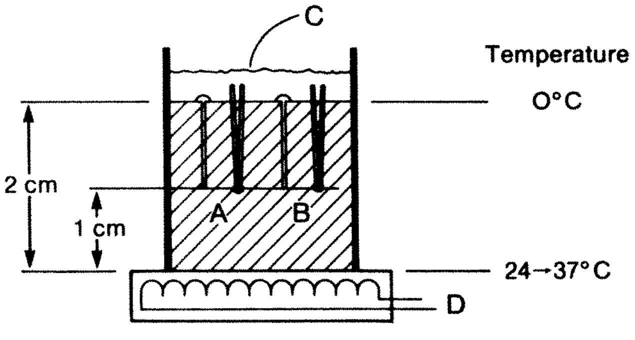

Fig 3. Temperature probe comparisons: temperature probe "stem effect," in vitro. A 2-cm-thick slab of beef heart is illustrated by the diagonal lines. The heart is placed on a hot plate labeled D, as illustrated by the coil. In the first comparison (A), a plastic temperature probe is placed adjacent to a bare thermocouple at a depth of 1 cm. In comparison B, a metallic temperature probe is placed adjacent to a bare thermocouple, also at 1 cm. Saline slush solution (C) is placed on top of the beef heart while the temperature of the hot plate is increased from room temperature (24°C) to 37°C. Temperature changes were recorded continuously over the range of 0° to 37°C.

Table 1. Results of Cardiac Hypothermia in an Acute Swine Model Using Cold Cardioplegia and Systemic Hypothermia (No Topical Cooling)[a]

Time	RVM	LVE	LVM	SEP
T_0	10.8 ± 2.7	10.0 ± 2.0	8.4 ± 1.8	8.2 ± 2.1
T_{10}	18.6 ± 4.1	19.9 ± 3.7	19.5 ± 3.6	19.1 ± 4.4

[a] All values are mean ± standard deviation (°C) (N = 12). Differences in T_0 values are significant at RVM and LVE versus LVM and septal sites (analysis of variance, $p < 0.005$). T_{10} value differences between sites are not significantly different by analysis of variance. Temperatures at all sites at T_{10} are significantly different than same sites at T_0 (analysis of variance $p < 0.005$).

LVE = left ventricular epicardium; LVM = left ventricular endocardium, myocardium, or cavity; RVM = right ventricular endocardium, myocardium, or cavity; SEP = interventricular septum; T_0 = cardiac temperatures immediately after cold cardioplegia infusion; T_{10} = cardiac temperatures 10 minutes after cardioplegia infusion.

Comment

Temperature Probe Design

Simultaneous measurement of epicardial and endocardial (myocardial or cavity) temperatures helps provide information about the sources of rewarming (internal, external, or both) by indicating transmural heat flows. Fourier's Law of Heat Conduction [23] states that the heat flux (heat flow per unit cross-sectional area in calories/min · cm^2) is proportional to the transmural temperature gradient (°C/cm) by a constant called the thermal conductivity (calories/min · cm · °C). Because the thermal conductivity of plastic is 75 times less than that of steel [23], the plastic probe can document transmural temperature differences more accurately. This occurs because the metal probe transfers more heat than a plastic probe by conduction along the "stem" from warm regions to colder regions, resulting in less accurate temperature measurements at a specific site. We have characterized this as the "stem effect." Thus, if myocardial temperatures are measured in the setting of temperature gradients of about 5°C/cm, it is expected that the metal probe will read 1.25°C less than the actual myocardium because the metal probe rapidly conducts heat from the interior. Similarly, a plastic probe will read 0.2°C greater than the actual value because the plastic probe reduces the amount of heat flow compared to the muscle. Because transmural gradients are on the order of a few degrees, better accuracy was obtained with the plastic probes. In addition, the plastic probe is pliable and may be less traumatic to the myocardium than metal probes if the probes are accidentally torqued while in place. However, the low profile of the probe head minimizes the probability of this occurrence.

Rationale of Temperature Monitoring

Myocardial rewarming occurs from both internal and external sources. Convection from systemic and pulmonary venous return is the internal cause, whereas external sources are radiation from the operating room lights and air as well as conduction from adjacent structures such as the aorta posteriorly, lungs laterally, and liver diaphragmatically [24].

Three separate probes have been fabricated to assess these areas. The RV probe is positioned anteriorly and contains a thermocouple near the hub to measure surface temperature, which may be affected by the operating room air and lights. The thermocouple near the tip is in or near the RV cavity to detect warming from systemic venous return. The LV probe is placed posteriorly or inferiorly. The thermocouple near the hub senses rewarming from the adjacent structures, and the thermocouple at the tip is affected by pulmonary venous return blood. The septal probe is inserted near the LV apex and positioned in the interventricular septum to detect overall maintenance of myocardial hypothermia (see Figs 1, 2).

Detection of Myocardial Rewarming in Porcine Hearts

After the completion of hypothermic cardioplegia administration and temperature equilibration, RVM temperatures were significantly warmer than LVM temperatures. One explanation is that because caval tapes were not used, systemic venous blood may not have been completely removed by the caval cannulas. Therefore, relatively small amounts of blood at systemic temperatures (28°C) entering the right ventricle could account for less cooling of the RVM by the cardioplegia solution as will be discussed.

Also, the LVM and interventricular septum were significantly cooler than the LVE. This difference could be explained by the fact that the LVE was being continually rewarmed by adjacent cardiac structures, specifically the liver inferiorly and the aorta posteriorly [24]. Also, bronchial return flow into the left atrium and ventricle may have been less than systemic return flow to the right side of the heart.

Clinical Inferences

MYOCARDIAL COOLING BY CARDIOPLEGIA. The ability to measure cardiac temperatures continuously at multiple sites allows more precise description of myocardial hypothermia. For example, the heat transfer capability of cardioplegia is exemplified by considering an average heart of 380 g [25] that is cooled from 30° to 15°C. Taking the specific heat of heart muscle to be about 1 calorie/g · °C (value for water), the net heat transfer is 5,700 calories (30° to 15°C). Given that the average rate of cardioplegic infusion is 4 minutes, the heat transfer rate is 1,425 calories/min. Other investigators have measured heat transfer associated with cardioplegia in dogs with normal coronary vessels and determined that about 12.3 calories/g of heart was removed [26]. If this result is extrapolated to the 380-g human heart, it corresponds to 4,864 calories (within 15% of the above value). The efficiency of the heat transfer capability of cardioplegia can be approximated by considering the process as a mixture problem in that all the heat gained by the cardioplegic solution equals all the heat lost by the heart (see next section). In support of this is a previous study of cold cardioplegia in dogs [27] wherein it was found that the coronary sinus temperature was considerably warmer than myocardial temperatures, indicating significant heat transfer had occurred.

HEAT TRANSFER AFTER CARDIOPLEGIA. The values of the regional and transmural temperature differences are important because they are related to the amount of heat transferred per unit area (heat flux) by conduction occurring after the administration of the cardioplegic solution. Temperature measurements may indicate rewarming of the right ventricle. A clinical study [14] indicated that without caval tapes, rewarming of the RVE occurred at 0.5°C/min with a temperature gradient of 5.5°C/cm. The heat flux can be calculated by assuming the thermal conductivity constant of myocardium to equal that of water, 1.4×10^{-3} calories/s · cm · °C [23]. Consequently, the heat flux for the right ventricle would be 0.5 calories/min · cm^2. For an RV surface area of 200 cm^2, the total heat transfer would be 100 calories/min. Additionally, heating from operating room lights by radiation may add 0.2 calories/min · cm^2 [17]. Assuming the net perpendicular area of the right ventricle that is heated by radiation is 50 cm^2, 10 calories/min are added. Consequently, rewarming of the right ventricle without caval tapes and local myocardial hypothermia may occur at 110 calories/min (Fig 4A). Also assuming that this rewarms the entire RV mass and the RV mass is about one-third of the total heart mass or 127 g, the RVM would rewarm at 0.86°C/min, which is very close to the actual value.

Because net heat flows from RVM to RVE, internal rewarming must be occurring. To estimate this, we assume that the rewarming of the endocardium is due entirely to rewarming of the blood within the right ventricle, which we have set equal to 150 mL. Because rewarming occurs at 0.5°C/min, 75 calories/min are required. A venous return of only 20 mL/min returning at 31°C (the approximate temperature of systemic venous blood) could account for this. Thus, in a typical case, the RVE rewarms 90% by conduction from the interior, plus 10% from the lamps, whereas RVM rewarms entirely by venous return. Consequently, the necessity to use caval tapes to prevent internal rewarming of the right ventricle is emphasized.

From the same clinical study [14], temperature data of the left ventricle revealed a small transmural gradient from the epicardium to the myocardium suggesting that the epicardium rewarmed by conduction from the adjacent surfaces, especially the posterior left ventricle. Using similar computations as above, the LVE rewarms at about 100 calories/min and the endocardium rewarms by pulmonary venous return at about 45 calories/min (only 5 to 10 mL/min of flow could explain this). Consequently, if a topical method is not used, a significant gradient from LVE to LVM of 5.5°C/cm occurs, which adds another 100 calories/min to the LVM by conduction (see Fig 4B). This illustrates the necessity of topical cooling methods to prevent LVM rewarming.

Continuous monitoring of cardiac temperatures at selected sites is facilitated by plastic temperature probes that have been specifically designed and fabricated to detect the various causes of myocardial rewarming. Prevention

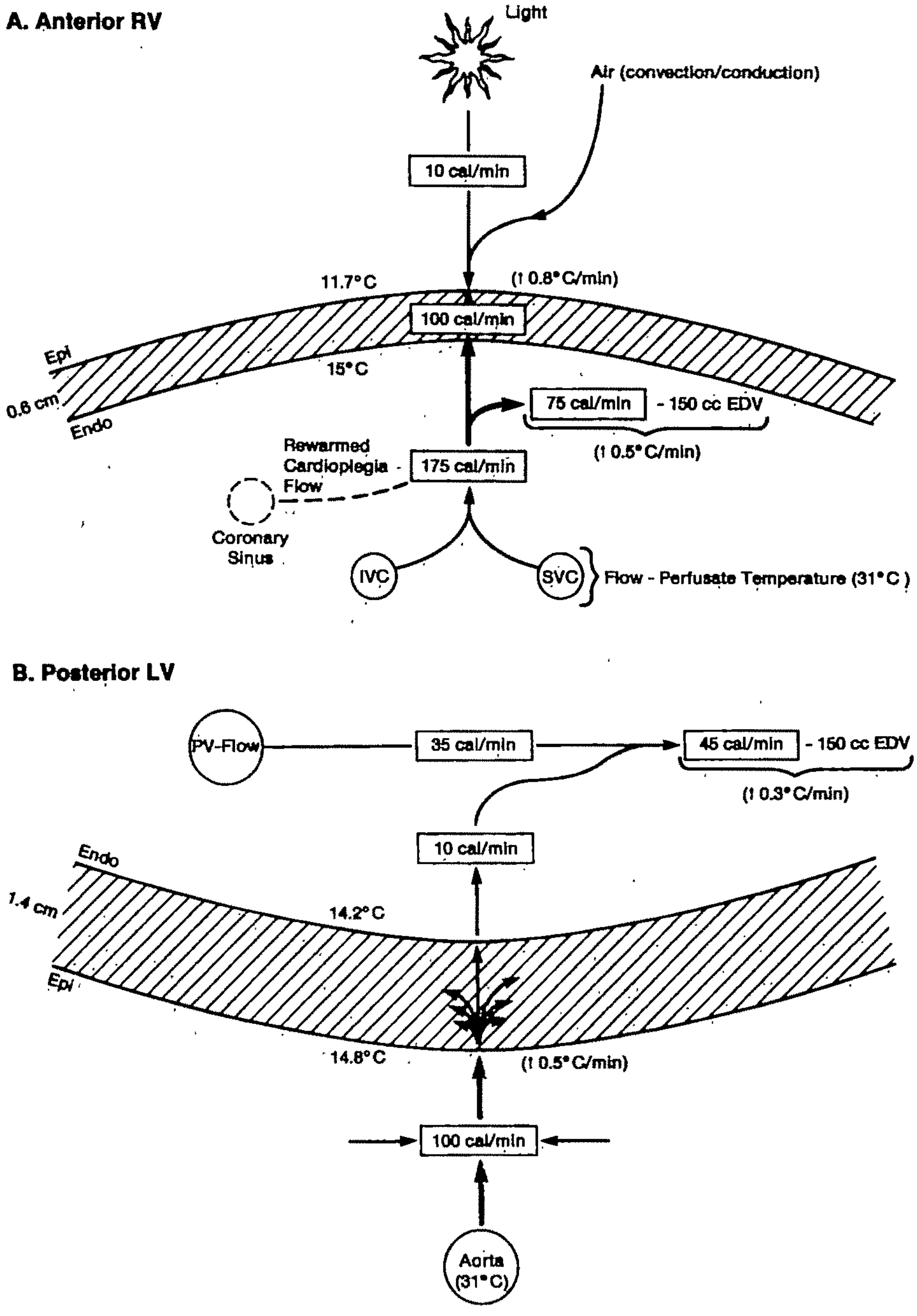

Fig 4. (A) Right ventricular rewarming: in a patient undergoing mitral valve replacement, the right ventricular epicardial temperature was found to be 11.7°C and the endocardial temperature was 15°C. With the systemic perfusate temperature at 31°C and failure to control systemic venous return, it is seen that heat flow is 100 calories/min to the right ventricular myocardium from systemic venous return while the operating room lights and air transfer an additional 10 calories/min. (B) Left ventricular rewarming: from the same procedure as in (A), the left ventricular temperatures are as represented. From the structures adjacent to the left ventricle (LV) *including the aorta, heat transfer is 100 calories/min while an additional 45 calories/min is transferred by the pulmonary venous* (PV) *return.* (EDV *= end-diastolic volume;* IVC *= inferior vena cava;* RV *= right ventricle;* SVC *= superior vena cava.)*

of rewarming allows optimization of myocardial hypothermia.

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Optimizing Myocardial Hypothermia: II. Cooling Jacket Modifications and Clinical Results

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After induction of myocardial hypothermia by cold cardioplegic solution, myocardial rewarming occurs at 0.5° to 1.0°C/min. In addition to preventing myocardial rewarming from systemic and pulmonary venous return, continuous cooling of the myocardial surface must be provided. Modifications of a previously reported cooling jacket are described. These modifications include decreased width and thickness of the metal skeleton for easier application and increased malleability, respectively. Also, the double-row flow channel markedly minimizes obstruction of flow secondary to kinking and allows inlet and outlet lines to attach at adjacent points of the jacket thus minimizing obstruction of the operative field. The effectiveness of the jacket in 36 patients undergoing valve replacement and 19 patients having pulmonary thromboendarterectomy was evaluated by measurement of myocardial temperatures at multiple sites throughout aortic cross-clamping. Temperatures at all sites were maintained at 12°C or less. Temperatures measured in phrenic nerve pedicles ranged from 25° to 27°C. During cooling, heat removal by the jacket was 330 calories/min. During maintenance of myocardial hypothermia, heat flow was 190 calories/min. Modifications of a cooling jacket facilitate usability and an array of sizes enhances applicability.

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Myocardial hypothermia during cardiac procedures is recognized as an important aspect of myocardial protection [1–4]. However, topical methods with saline irrigation are associated with inconsistent and suboptimal myocardial temperatures [5–7]. Saline slush has been associated with phrenic nerve paresis [8–10] and myocardial damage [11]. Cooling jackets to provide more even distribution of the coolant have been described [12, 13]. Hemodilution and blood loss associated with the saline irrigant are eliminated but a substantial incidence of phrenic nerve paresis has been reported with the Bonchek-Shiley cooling jacket [8], whereas the Cobe cooling jacket has been associated with suboptimal cooling [14].

Previously, we reported the use of a cooling jacket in a comparative study of methods of myocardial hypothermia [13]. The purpose of this report is to describe subsequent modifications of the cooling jacket and its use in an extended series of patients undergoing valve replacement and pulmonary thromboendarterectomy.

Material and Methods

Description of Cooling Jacket

To maintain myocardial hypothermia, we have designed a jacket that consists of flexible polyurethane sheeting (0.254 mm thick) that has been welded into two rows of channels for conduction of cooling fluid (Fig 1). Polyurethane was selected because of maintenance of flexibility at temperatures near 0°C. The shape of the cooling jacket was designed to cover as much of the ventricles as possible, thus maximizing myocardial cooling as well as minimizing rewarming from surrounding structures. The basic jacket construction consists of three layers (see Fig 1). The innermost layer, which lies adjacent to the heart, consists of channels through which cooling fluid is pumped. The coolant flow circuit has been specifically designed in two rows to minimize obstruction to coolant flow even with severe distortion of the jacket. Also, the two-row design allows both inlet and outlet tubes to be adjacent, thereby minimizing obstruction of the operating field. The second (center) layer contains a thin, malleable metallic backbone that allows easy intraoperative molding of the jacket to conform to the right and left ventricles. The metal skeleton has been reduced in width to facilitate application of the cooling jacket and decreased in thickness to increase malleability. Additionally, a gap may be left between the edges of the cooling jacket for performance of coronary artery bypass grafting [15]. The third (external) layer consists of a 1.58-mm-thick polyethylene foam insulation, which minimizes cardiac rewarming from external structures and excessive cooling of the phrenic nerves. The three layers are entirely enclosed in polyurethane sheeting resulting in a topical cooling jacket of integral construction that is easy to apply, maintains its shape, and has a thin cross-sectional profile (see Fig 1).

The cooling circuit to which the jacket is attached is shown in Figure 2. The system is initially purged of air with sterile saline solution from a 500-mL intravenous bag, which can be removed after purging. Cooling is

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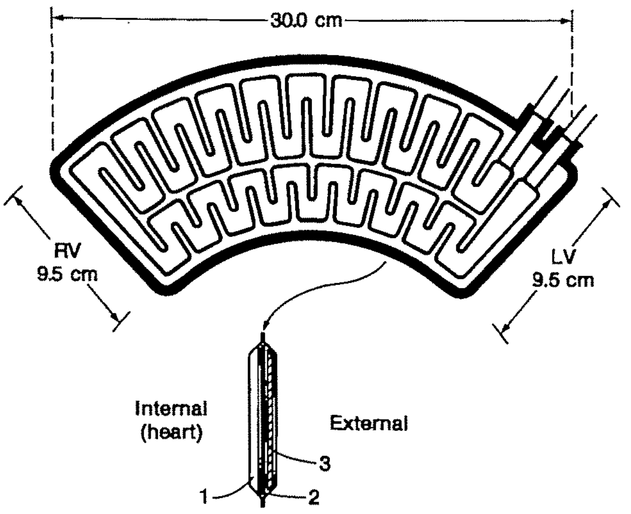

Fig 1. Cooling jacket construction: the inner aspect of the cooling jacket contains the coolant flow path, labeled 1. 2 *represents the locations of the metal skeleton, and* 3 *represents the location of the polyurethane insulation.* (LV = *left ventricle;* RV = *right ventricle.)*

provided by a cooling coil immersed in saline slush. The pumping force is provided by a roller pump. The system is typically set up and purged by the perfusionist and scrub nurse so that it is ready for cooling as soon as the jacket is placed in position. An array of six different sizes of cooling jackets has been fabricated and is depicted in Figure 3. Their dimensions are described in Table 1.

Clinical Evaluation

After initial prototypes had been tested, a clinical research protocol for the cooling jacket was submitted to our institutional review board and approved. The cardiac cooling jacket was used in 55 patients (36 valve replacements and 19 pulmonary thromboendarterectomies) (Table 2) with multisite temperature monitoring [15] and continuous recording.*

Before institution of cardiopulmonary bypass, plastic temperature probes [16] were inserted into standardized locations: right ventricular epicardium and myocardium or cavity, left ventricular epicardium and myocardium or cavity, and septum as previously described [15]. Moderate systemic hypothermia at 28°C was maintained in the valve replacement patients. After aortic cross-clamping, 1,000 mL of cardioplegia was infused into the aortic root at 5° to 7°C. Frequently, before reduction in the width of the metal skeleton to enhance exposure, the jacket was applied after the aortic or mitral valve, or both, were removed and the annuli were sized resulting in a 3- to 15-minute period before the cooling jacket was applied. Subsequent to the changes in the metal skeleton, the jacket has been applied *before* cross-clamping. Pulmonary artery venting was routinely used to minimize pulmonary venous drainage into the left atrium and ventricle. Only single-dose cardioplegia was used and no topical cooling methods, other than the jacket, were employed after cardiac hypothermia had been initiated.

In the patients undergoing pulmonary thromboendarterectomy, systemic hypothermia was 20°C or less, and the jacket was usually applied before cardioplegic infusion. Standard cardiopulmonary bypass with bicaval cannulation and caval snares was used in both valve replacement and pulmonary thromboendarterectomy patients.

The temperatures at all five sites in each patient were graphically analyzed from the readings of the temperature probes [13, 16]. The data were analyzed by computing the average temperatures at each of the five sites at the following times: at cross-clamp but before cardioplegic infusion

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* Omega Cold Junction Compensator No. CJ, Omega Thermocouple Amplifier Model OMNI-1, Omega Model 650, Omega Engineering, Inc, Stamford, CT; Hewlett-Packard eight-channel recorder, Model 7758, Hewlett-Packard Company, Andover, MA.

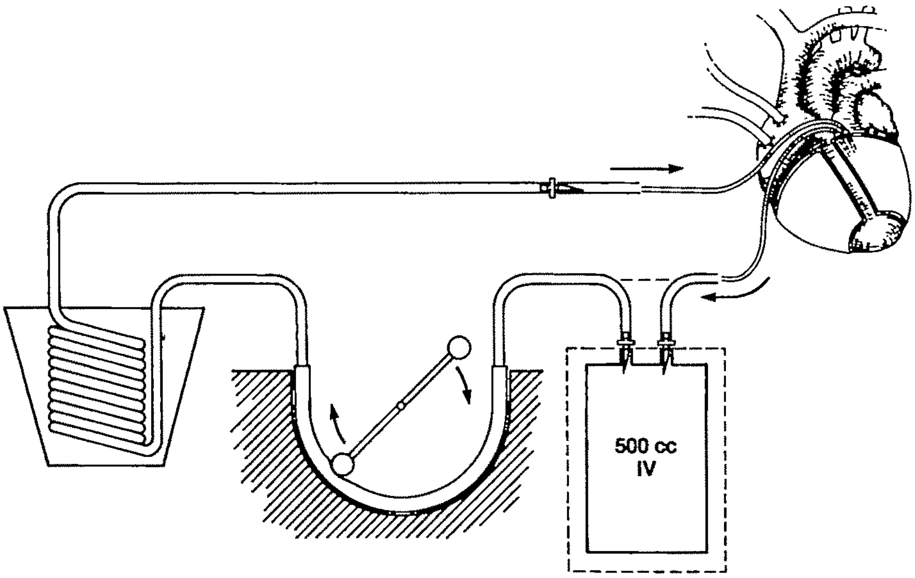

Fig 2. Cooling circuit of the jacket: the coil is immersed in saline solution to which alcohol can be added to obtain lower temperatures of the coolant. The bag of normal saline solution (500 cc IV) is used to prime the circuit and remove air.

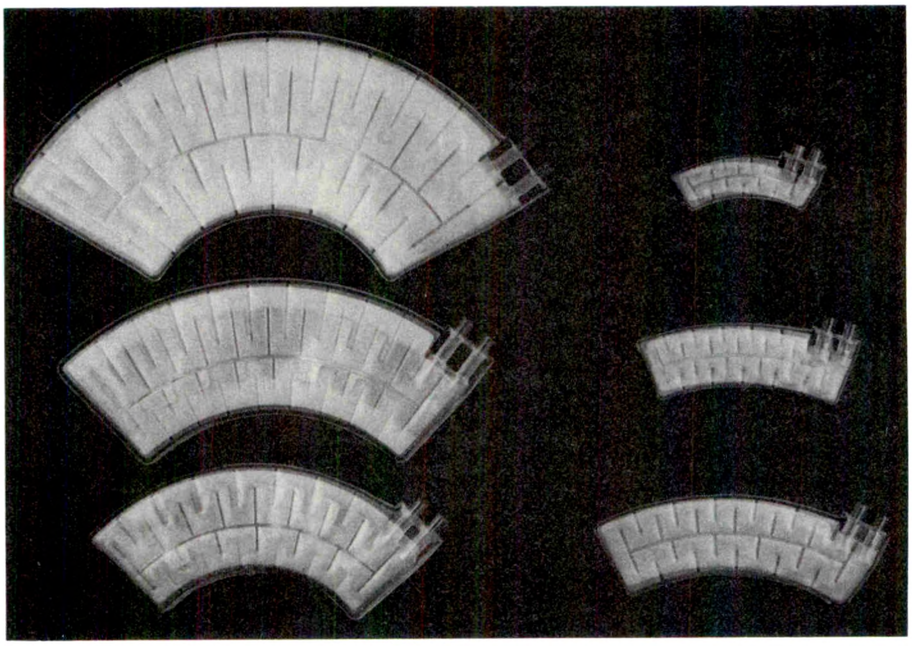

Fig 3. Jacket sizes: six sizes of the jacket including three pediatric and three adult sizes are shown. The exact sizes are described in Table 1.

(defined as time 0), immediately after cardioplegic infusion, 10 minutes after jacket application, 20 minutes after jacket application, 30 minutes after jacket application, and at the time the jacket was removed. Transmural temperature differences were computed for the 36 valve replacement patients after 10 minutes and 30 minutes of jacket application between the left ventricular epicardium and left ventricular myocardium or cavity and the right ventricular epicardium and right ventricular myocardium or cavity to estimate the direction and amount of heat removed by the cooling jacket.

Temperatures of the phrenic nerve pedicles were measured in 2 patients during valve replacement with bare thermocouples while the jacket was in place to determine the protective effect of the jacket insulation.

In 1 patient temperatures at the jacket inlet and outlet were recorded continuously in addition to the other five sites.

Results

Valve Replacement

Figure 4 summarizes the cardiac hypothermic profiles obtained with the topical cooling jacket in 36 valve replacement patients. Infusion of cold cardioplegia is associated with a relatively rapid drop in all the cardiac temperatures (average infusion time, 4.8 minutes). Rewarming started as soon as the infusion was completed. Application of the jacket at 9.4 minutes (average) caused temperatures to decrease at all five sites. The initial effect of the topical cooling jacket occurs predominately on the epicardial surfaces. Because epicardial temperatures at both ventricular sites were less than myoendocardial temperatures, heat was being removed by the jacket; consequently, the myoendocardial and septal temperatures also decreased, but more slowly. With increasing cross-clamp times the temperatures stabilized indicating steady state (net heat flow in = net heat flow out of jacket). At this point all cardiac temperatures averaged less than 11°C. The average cross-clamp time was 65.3 ± 27.4 minutes (± standard deviation) with a range of 22 to 140 minutes.

Left Ventricular and Right Ventricular Transmural Gradients

The left ventricular and right ventricular transmural temperature differences and gradients after 10 and 30 minutes

Table 1. Cooling Jacket Dimensions

Size[a] (cm)	Greater Curvature[b] (cm)	Lesser Curvature[b] (cm)	Width[b] (cm)
8	10.2	7.5	3.0
12	14.8	11.6	4.5
16	20.0	14.5	5.7
23	23.8	13.5	7.6
28	29.8	17.5	9.4
36	37.0	16.3	12.5

[a] Straight-line measurement as shown at top of Figure 1. [b] The greater curvature, lesser curvature, and width are illustrated in Figure 1.

Table 2. Case Summary for Clinical Evaluation of the Topical Cooling Jacket

Operation	With CABG	Without CABG	Total
MVR	4	8	12
AVR	4	10	14
MVR + AVR	. . .	10	10
PTEA			19
Total			55

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; PTEA = pulmonary thromboendarterectomy.

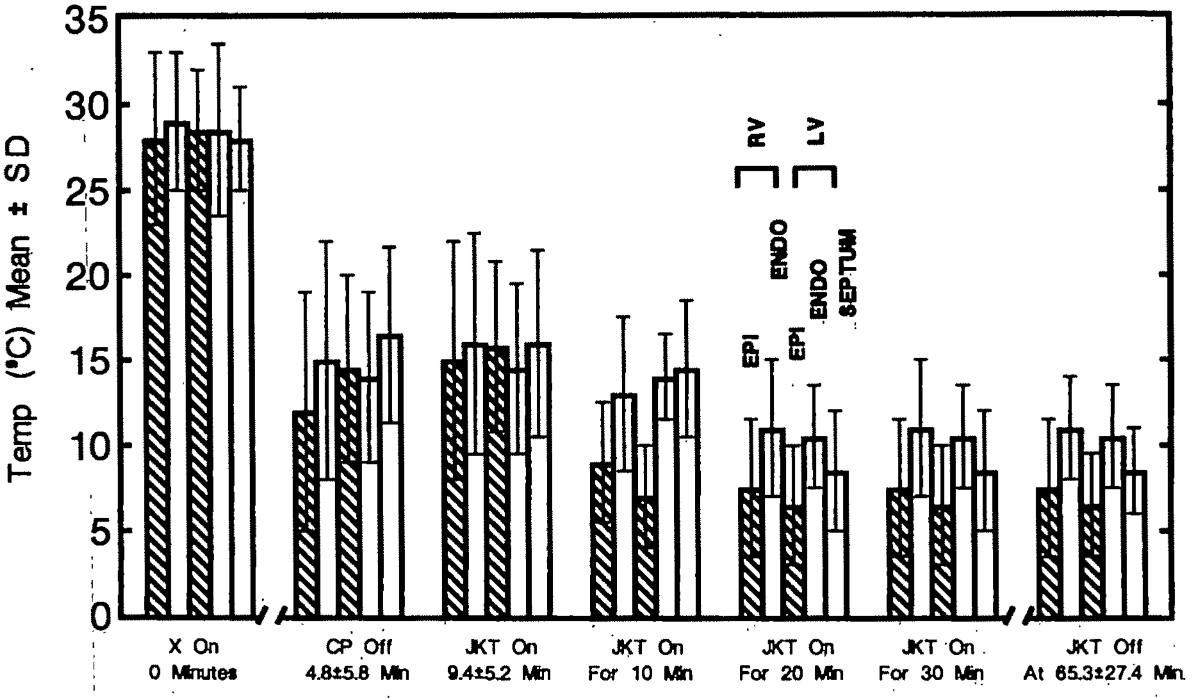

Fig 4. Temperatures in 36 patients undergoing valve replacement: all temperatures are mean temperatures ± standard deviations (SD). (CP = cardioplegic solution; ENDO = myocardium or cavity; EPI = surface or epicardial temperature; JKT = jacket; LV = left ventricle; RV = right ventricle; SEPTUM = interventricular septum; X = application of aortic cross-clamp.)

of jacket cooling in 36 valve replacements are summarized in Table 3. At both times, right ventricular and left ventricular myocardium or cavity temperatures exceeded their respective epicardial temperatures.

Pulmonary Thromboendarterectomy

Figure 5 summarizes the cardiac temperature profiles obtained with the topical cooling jacket in 19 pulmonary thromboendarterectomies. The results are similar to those for valve replacement. In about two-thirds of the cases, the jacket was applied before the infusion of cardioplegia, which tended to reduce the rewarming trend seen after cardioplegic infusion. Application of the jacket initially reduced the epicardial temperatures while the endocardial (right and left ventricular) and septal temperatures decreased in a delayed fashion. As steady state was achieved, the average cardiac temperatures were less than 9°C. The average cross-clamp time was 108 ± 87 minutes (±standard deviation) with a range of 25 to 186 minutes.

Table 3. Transmural Temperatures Measured During Use of the Topical Cooling Jacket in 36 Valve Replacements

	Right Ventricular		Left Ventricular	
J_{on} (min)	Myo − Epi (°C)	Gradient (°C/cm)	Myo − Epi (°C)	Gradient (°C/cm)
10	3.3 ± 6.1	5.5	5.5 ± 3.3	3.9
30	1.5 ± 2.0	2.5	3.8 ± 1.9	2.7

Epi = epicardial or surface temperatures; J_{on} = time of application of jacket; Myo = endocardium, myocardium, or cavity temperatures.

Phrenic Nerve Temperatures

The phrenic nerve temperature results obtained during cardiac hypothermia in two valve replacements are presented in Table 4. The temperatures of the phrenic nerves were between 25° and 27°C when the jacket was in place and cardiac temperatures were between 6° and 15°C.

In a sample case, measurement of the inlet and outlet temperatures of the jacket when the jacket was first applied revealed the inlet temperature to be 5.6°C and the outlet temperature, 6.7°C. Because the flow rate through the jacket was about 300 mL/min, the heat exchange across the jacket was: [(1 calorie/g · °C) (300 mL/min) (1 g/mL) (1.1°C)] = 330 calories/min. With time, the temperature difference across the jacket was reduced and a relatively steady state was achieved. By calculations similar to those above, steady-state heat removal by the jacket was 190 calories/min.

Comment

Design of Cooling Jacket

The shape of the cooling jacket was designed to afford maximal contact with the surfaces of the left and right ventricular muscle mass. This shape was determined after numerous measurements during cardiopulmonary bypass. With the heart decompressed, the distance from the atrioventricular groove to the apex was measured along the acute and obtuse cardiac margins. Also, the circumference at the greatest diameter of the ventricular mass was measured. An additional consideration was the use of an insulator pad contained within the jacket envelope to minimize both rewarming of the myocardial tissue and

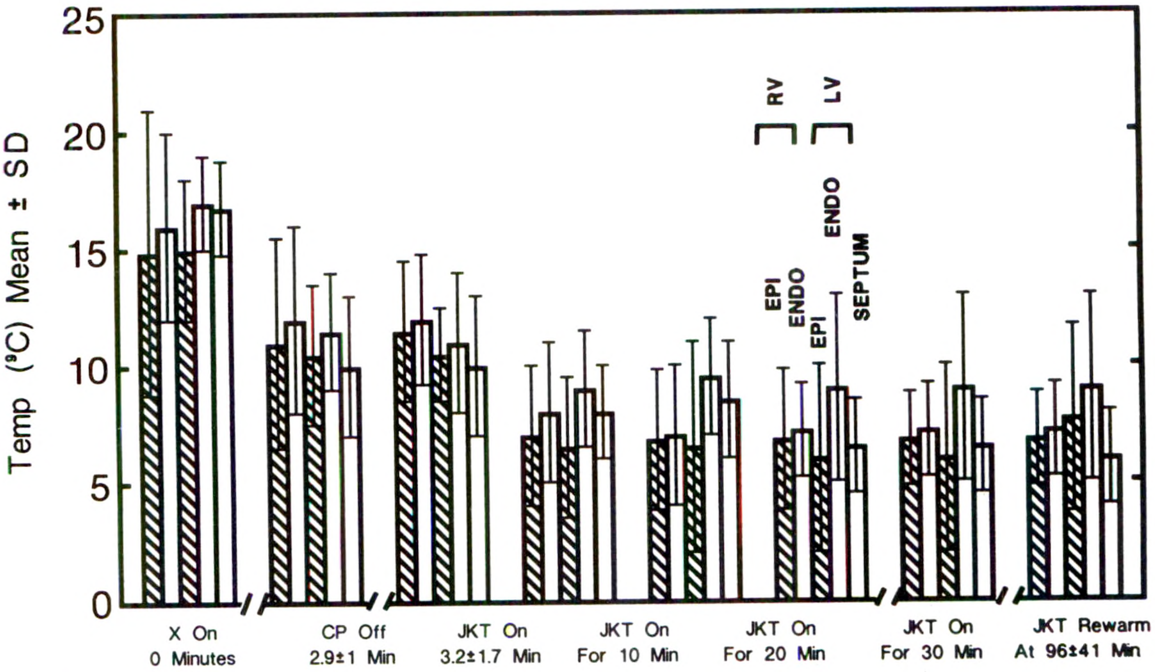

Fig 5. Temperatures in 19 patients undergoing pulmonary thromboendarterectomy: all temperatures are mean temperatures ± standard deviations (SD). (CP = cardioplegic solution; ENDO = myocardium or cavity; EPI = surface or epicardial temperature; JKT = jacket; LV = left ventricle; RV = right ventricle; SEPTUM = interventricular septum; X = application of aortic cross-clamp.)

excessive cooling of the phrenic nerves. During most cardiac procedures, there is no contact between the cooling jacket and the right phrenic nerve area. As seen from the phrenic nerve temperatures that were recorded and the relative rarity (1%) of phrenic nerve paresis in our more recent experience [17], it would appear that this design feature is relatively effective in minimizing phrenic nerve paresis from excessive hypothermia.

Another consideration was the use of a malleable metal skeleton in the center of the jacket to maintain contact of the cooling coil of the jacket with the ventricular mass without the necessity to have a locking mechanism to secure the jacket in place. It is advantageous to be able to spread the ends of the jacket to allow coronary artery bypass grafting as has been previously described [15]. Recent changes have resulted in reduced width of the metal skeleton to allow increased ease of application of the jacket and also in decreased thickness of the metal skeleton to increase malleability and, yet, maintain the desired shape. The two rows of coolant flow channels allow severe distortion of the jacket without obstruction of coolant flow. Also, the inlet and outlet are adjacent at one end of the jacket, which minimizes obstruction of the operating field.

Advantages of the Cooling Jacket for Myocardial Hypothermia

The primary advantage for use of a cooling jacket is to ensure apposition of flow channels to essentially all of the surface area of the right and left ventricular myocardial mass to obtain more consistent and complete cooling. Comparison with continuous pericardial irrigation with hypothermic saline solution reveals that with the cooling jacket myocardial hypothermia is more consistent, with respect to various areas of the myocardium, and lower temperatures are maintained [7, 15]. Additionally, there is no need for continuous aspiration of the saline solution, which produces substantial noise and at the same time may result in continual blood loss from the operative field. Also, the saline irrigant may be aspirated into various cardiac chambers and returned to the cardiopulmonary bypass circuit resulting in some degree of he-

Table 4. Summary of Phrenic Nerve Temperature Measurements

Patient No.	Operation	Range of Cardiac Temperatures (°C)	Systemic Temperatures[a] (°C)		Phrenic Temperatures[a] (°C)	
			NP	Other	Left	Right
1	MVR	6–9	30.0	32.0[b]	25.2	27.0
2	MVR + CABG	9–15	30.2	31.1[c]	25.6	26.7

[a] Temperatures measured 30 minutes after jacket application. [b] Rectal temperature. [c] Blood temperature.

CABG = coronary artery bypass grafting; MVR = mitral valve replacement; NP = nasopharyngeal.

modilution. Consequently, both blood loss and hemodilution are eliminated with the use of the cooling jacket and the operative field is relatively quieter and dryer. In short, the advantages of the cooling jacket are as follows:

1. Uniform, profound (6° to 12°C) myocardial hypothermia
2. Prevents myocardial rewarming
3. Protects phrenic nerves
4. Ease of use
5. No saline disposal problem
6. Dryer operative field
7. Minimizes blood loss
8. Minimizes hemodilution
9. Noiseless
10. Can be used in virtually all types of cardiac operations requiring aortic cross-clamping

Effectiveness of Cooling Jacket

Prolonged cardiac hypothermia depends on minimizing internal and external rewarming sources as indicated by the cardiac temperature measurement system [16] and on providing continuous surface cooling. The relatively high heat flows that can occur with cardioplegic infusion (1,425 calories/min [16]) indicate why this method is preferred for initiation of cardiac hypothermia. However, the cooling jacket is more than adequate for maintenance of myocardial hypothermia, as seen in the following analysis. With an average rewarming rate, after cardioplegia, of 0.5°C/min in a 380-g heart, the heat flow would be 190 calories/min [18, 3]. With an average flow rate through the jacket of 300 mL/min and average inlet/outlet temperature difference of 1.1°C, heat removed by the jacket is 330 calories/min. The excess heat removed of 140 calories/min can result in a cooling rate of 0.4°C/min. Consequently, in addition to neutralizing cardiac rewarming, the cooling jacket can result in a myocardial cooling rate of 0.4°C/min (for a 380-g heart).

The left ventricular and right ventricular transmural gradients after 10 minutes of jacket application were 3.3 and 5.5°C/cm, respectively. Using 5°C/cm as an average gradient and similar assumptions as reported elsewhere [16], the heat flux was 0.4 calorie/min · cm^2. Assuming a net ventricular surface area of 432 cm^2, the net heat flow was 173 calories/min, which approximates the net rewarming rate of 190 calories/min as determined in the results. The cooling jacket has its initial effect on the epicardial surfaces, which are cooled quickly, creating a transmural gradient. The gradient consequently causes heat flows that cool the endocardial and septal sites. The steady net heat flow of 190 calories/min requires that topical methods be applied continuously rather than intermittently. Therefore, it is desirable to apply the jacket before aortic cross-clamping to optimize effectiveness of cooling with the cardioplegic solution and to prevent the immediate rewarming that begins as soon as cardioplegic solution delivery is completed.

Consequently, it is apparent that if internal rewarming is minimized by control of systemic and pulmonary venous return, the use of a cooling jacket can maintain myocardial temperatures at 12°C or less throughout aortic cross-clamping.

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Diagnosis of Poststernotomy Infection: Comparison of Three Means of Assessment

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Of 737 adults undergoing cardiac operations through a median sternotomy over a 2-year period (January 1988 to January 1990), sternal-substernal space infection requiring mediastinal exploration developed in 8. Six of these patients as well as 18 additional patients were evaluated for possible poststernotomy wound infection by computed tomography (4 true positive, 4 false positive, 10 true negative, 2 false negative), indium-111 leukocyte scanning (5 true positive, 0 false positive, 18 true negative, 1 false negative), and epicardial pacer wire cultures (6 true positive, 1 false positive, 12 true negative, 0 false negative). On the basis of this experience it is suggested that in addition to computed tomography, indium-111 leukocyte scanning and epicardial pacer wire cultures may be useful in the diagnosis of poststernotomy deep wound infection.

(Ann Thorac Surg 1991;51:290–2)

Continued interest in the problem of sternotomy wound infection after cardiac operations reflects the persistence and gravity of this problem. The pathogenesis, diagnosis, and management of this complication have been reviewed recently [1–4]. Although the diagnosis of the presence and extent of sternotomy wound infection is often straightforward, this is not always so [5]. That timely diagnosis is important has been established [6]. Since the report of Kay and associates [7], computed tomographic (CT) scan of the chest has become an accepted diagnostic maneuver when sternotomy wound infection is suspected. Similarly, the usefulness of various modifications of aspiration of the substernal space has been pointed out [6].

As has been noted [7], CT scan in the early postoperative period (10 to 14 days) often shows nonspecific changes in cardiac surgical patients. Although we have found this technique to be of value on occasion, we also have found it to produce nonspecific and sometimes misleading results in the early postoperative period.

After noting reports such as those of Goodwin [8] and Babar and co-workers [9] and at the suggestion of two of us (R.W.B. and M.F.), we decided to investigate the usefulness of indium-111 leukocyte scans (ILSs) in patients suspected of harboring deep sternal wound infections.

Approximately 8 years ago one of us (D.A.B.) had occasion to do a series of epicardial pacer wire cultures (EPWCs) during investigation of newly designed epicardial pacer wires (unpublished data, Medtronic, Inc, Minneapolis, MN). During this study, 38 patients had pacer wire cultures done (postoperative days 5 to 12). Thirty-seven of these were true negative and one was false positive (*Staphylococcus epidermidis*). None of these patients developed infection. This experience suggested that epicardial wires were not often a cause of infection, and such cultures might be helpful in the early diagnosis of deep poststernotomy infection.

Material and Methods

For purposes of this study, poststernotomy infection was defined as wound infection involving the sternum and substernal space. Infections confined to the more superficial tissues were not considered. Patients were considered positive for deep wound infection if found to have positive findings and cultures at the time of formal exploration of the mediastinum.

Patients were selected for study by their surgeon when poststernotomy infection was suspected but immediate exploration was not believed justified. This basis for suspicion included wound findings (such as erythema, edema, drainage, possible instability, excessive pain, or tenderness) or systemic signs (such as fever, tachycardia, change in white blood cell count or differential). In patients in whom definite evidence of deep wound infection was believed to be present, exploration was undertaken immediately without preliminary study or with incomplete preliminary study.

Computed tomographic scans were obtained using Seimens devices with the use of intravenous contrast material at the discretion of the radiologists [10]. These scans were read by any of seven radiologists as "suspicious," "not suspicious," or "equivocal" for poststernotomy infection. The radiographers were not aware of the fact of this study. Findings including fluid collections, presence of gas, and sternal changes were noted.

Indium-111 leukocyte scanning was done using meth-

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ods described by Knochel and associates [11]. This technique involves the isolation of autologous leukocytes from 50 mL of blood sedimentation and centrifugation. These washed autologous white cells are labeled with indium 111, resuspended in autologous plasma, and returned to the patient by intravenous administration. Scans are then obtained at 4 and 24 hours using a gamma camera (Seimens). These scans were read as "suspicious" for infection or normal by any of seven staff radiologists based on tracer accumulation in the area of the sternotomy wound at 24 hours after intravenous injection of the labeled autologous white blood cells.

Epicardial pacer wire cultures were done on postoperative days 4 to 11 as follows: Before removal of epicardial pacing wires, the skin was prepared with povidone-iodine (Betadine) and allowed to dry. Using sterile technique the wires were removed, and the ends were cut off and placed in a sterile container. These were then cultured in the usual manner.

Results

During the period January 1988 to January 1990, 737 adult cardiac operations using median sternotomy and cardiopulmonary bypass were performed. Three patients underwent exploration for poststernotomy infection without preliminary study. One of these explorations was negative and two were positive (1 *Staphylococcus aureus* infection, 1 combined *Enterobacter* and *Candida albicans* infection). An additional 6 patients underwent exploration after preliminary studies; all of these explorations were positive (3 *Staphylococcus epidermidis*, 2 *Staphylococcus aureus*, 1 *Serratia marcescens*). Eighteen additional patients were suspected of harboring poststernotomy infection and underwent study but were not explored. To date (September 1990) none of these 18 patients has been found to have wound infection (100% follow-up).

Computed tomographic scan was truly positive in 4 patients and falsely negative in 2 patients; it was truly negative in 14 patients and falsely positive in 4 patients. Computed tomographic scans were done on postoperative days 5 to 15.

Indium-111 leukocyte scanning was truly positive in 5 of 6 infected patients and falsely negative in 1 patient. In 18 of 18 suspect, but not infected patients ILSs were truly negative. There were no false-positive ILSs.

Epicardial pacer wire cultures were truly positive in 6 infected patients. In each instance, the organism cultured was identical to that found at the time of exploration. In 18 suspect, but not infected patients, EPCWs were true negative in 14 and false positive in 1 patient. In 3 of the 18 suspect patients, EPWCs were not done, the wires having been removed before the patients were thought to possibly have infection.

Comment

Mediastinitis after cardiac operations remains a dreaded complication. Fortunately with prompt diagnosis appropriate therapy will allow survival in the majority of these patients.

Although sometimes obvious, infection deep within the sternotomy wound can be obscure in its presentation. This is especially true early in the postoperative period when other areas of potential infection exist and antibiotics have been administered. As noted during this study, 1 patient was explored for infection with a negative result: the explanation of the patient's fever, leukocytosis, and wound erythema and tenderness remains unknown. In addition, we have had the experience of discharging a patient after low-grade fever had subsided who returned in extremis from sepsis associated with obvious advanced mediastinitis 4 days later.

Although not encountered during this study, we have discovered unexpected infected aortic false aneurysms in 2 patients with very subtle signs of infection in the postoperative period by CT scanning on postoperative days 10 and 15. For this reason as well as its other uses, we continue to use this study in many patients when infection is suspected despite its limitations especially in the early postoperative period.

The uses of ILS in the diagnosis of local areas of bacterial infection involving soft tissues, bone, and vascular grafts have been reported [9, 12–18]. In our limited experience, ILS was false-negative in 1 patient. This 71-year-old diabetic man with chronic leukopenia (white blood cell count, 3.5×10^9/L [3,500/μL]) of unknown cause developed a *Serratia marcescens* mediastinitis after an emergency redo coronary artery operation. It has been noted in previous reports that ILS may be falsely negative in the presence of leukopenia or some forms of infection (such as *Serratia* infection), circumstances in which white blood cell mobilization and localization may be limited. In all instances, ILS at 24 hours was clearly "suspicious" or "not suspicious." An example of a "suspicious" true-positive scan is seen in Figure 1.

The potential usefulness of EPWC was suggested to us by the technique of sternal and substernal aspiration. Having had some experience with substernal aspiration, it seemed safe, and perhaps simpler, to culture the pacer wires. Although it presumably can occur, we have not encountered a situation in which we documented spread of infection from the temporary pacing wire site to the mediastinum. This may be because of our "compulsive" nursing services with frequent pacer wire site inspection and cleaning.

During this study one false-positive EPWC was encountered. This was done on postoperative day 6 in a 44-year-old man with persistent fever and leukocytosis after aortic valve replacement. Computed tomographic scan was also false positive, and ILS was true negative. He eventually was found to have cytomegalovirus infection from which he recovered.

When considering the use of these examinations, it is of interest to note the costs involved. In our hospital, CT scan costs $600; ILS, $370; and EPWC, $40. Computed tomographic scan radiation dosage is approximately 0.04 Gy, which is approximately equal to that received with an ILS.

A major failing of this study is the small numbers of patients involved. These numbers do not allow reliable

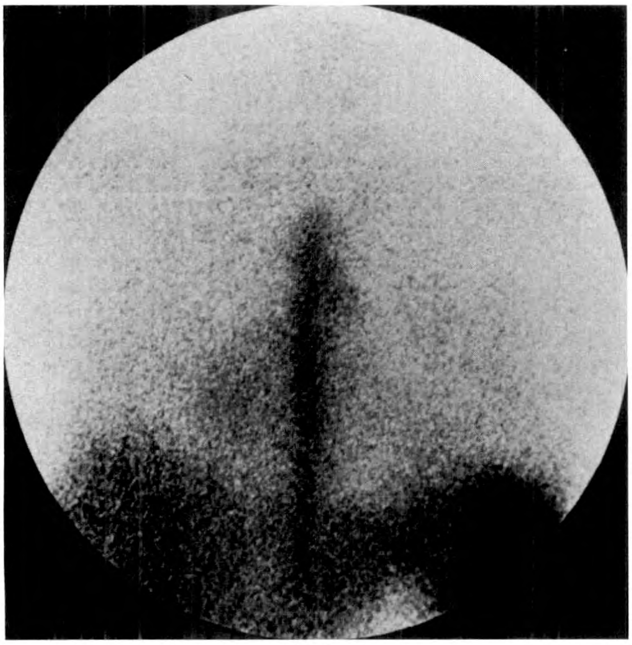

Fig 1. A "positive" ILS study at 24 hours after I^{111}-labeled autologous white cell injection in a patient proven to have a Staphylococcus epidermidis *mediastinitis at exploration on the eighth postoperative day.*

calculations of specificity and sensitivity for CT scan, ILS, and EPWC in cardiac surgical patients in whom infection of the mediastinum is suspected. This being the case, we can only suggest that, in addition to CT scan, ILS and EPWC may be helpful in the early diagnosis of some patients with poststernotomy wound infection. Further investigation of these approaches is believed indicated.

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Combined Superior-Transseptal Approach to the Left Atrium

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The combined superior-transseptal approach to the left atrium was used in 22 patients: to perform a mitral valve repair in 14 patients and mitral valve replacement in 8 patients. Mitral valve operation was combined with other cardiac procedures in 18 patients (82%) and was performed as a reoperation in 3 patients (14%). In all cases there was excellent exposure of the complete mitral annulus and subvalvar apparatus. There were no instances of postoperative bleeding, conduction defects, or intraatrial shunting related to the approach. The combined superior-transseptal approach to the left atrium is an excellent approach that can be used in most reoperations and primary procedures for isolated or combined mitral valve operations.

(Ann Thorac Surg 1991;51:293–5)

The success of any operation is influenced by the exposure of the tissues operated on. Operation on the mitral valve may be difficult when exposure is not satisfactory, as can be the case when the left atrium is not enlarged or when, after a previous procedure, the atrioventricular ring is fixed in a right anterolateral, left posteromedial position.

The ideal approach to the mitral valve gives an undistorted exposure of the complete mitral annulus and subvalvar apparatus from a short distance, without damage to the surrounding structures. We describe in this report our initial experience with such an approach.

Material and Methods

The mean age of the 22 patients that were operated on was 62 years, with a range of 29 to 79 years. Half of the patients were men and 5 patients (23%) had atrial fibrillation preoperatively. Table 1 shows the operative procedures performed, including 18 (82%) combined procedures and 3 (14%) reoperations on the mitral valve.

The heart was exposed in all patients by a median sternotomy. After heparinization, aortic cannulation was accomplished in the ascending aorta and the superior vena cava was cannulated directly by a 24F cannula with a short curved tip. The inferior vena cava was cannulated with a 28F cannula with a long curved tip. On complete bypass and moderate (28°C) hypothermia, the aorta was cross-clamped and 1 L of blood cardioplegic solution was given to arrest the heart. Both venae cavae were snared and the right atrium was opened obliquely lateral from the inferior venous cannula to the medial part of the right atrium where it meets the roof of the left atrium (Fig 1). Care was taken not to damage the sinus node at the lateral aspect of the right atrium. The medial and lateral parts of the right atrial wall were retracted by stay sutures. The interatrial septum was opened longitudinally at the fossa ovalis. This incision was carried caudally to the inferior limbus, and cranially the incision was continued through the roof of the left atrium in the direction of the left atrial appendage (Fig 2).

The exposure of the anterior part of the mitral annulus was facilitated by several retraction sutures. No retraction instruments were necessary for exposure (Fig 3). After the mitral valve procedure, the roof of the left atrium and the interatrial septum were closed with a continuous 3-0 or 4-0 monofilament suture. The right atrial wall was approximated with a running 4-0 or 5-0 monofilament suture. Both sutures were tied while the respective atrial chamber was filled with blood.

After air bubbles were removed from the right and left sides of the heart, atrioventricular pacemaker wires were left routinely and the patient was decannulated. Operative results were evaluated by an intraoperative transesophageal echocardiogram. All patients were followed up during their hospital course and in our clinics.

Results

The exposure of the left atrium and mitral valve, including both commissures as well as the subvalvar apparatus, was excellent in all cases. In no case was there damage of tissues that were not incised intentionally. Although the incisions and the closure of the tissues consumed slightly more time than by the conventional method of opening the left atrium from behind the interatrial groove only, we had the impression that the total operative procedure tended to take less time because of facilitation of the mitral procedure itself. There was no incidence of a bleeding complication due to the incisions made. No case of interatrial shunting was detected by intraesophageal echocardiogram. All 17 patients (77%) who had normal sinus rhythm before operation remained so after the procedure. Also, in the 5 patients (23%) with atrial fibril-

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Table 1. Operative Procedures

Procedure	No. of patients
Mitral valve plasty + CABG	8
Mitral and aortic valve replacement[a]	4
Mitral valve plasty	3
Mitral valve replacement	1
Mitral and tricuspid valve plasty	1
Mitral valve plasty and aortic valve replacement	1
Mitral valve replacement + CABG	1
Mitral valve plasty + myxoma left atrium	1
Mitral valve replacement + tricuspid valve plasty + CABG	1
Mitral valve replacement + myectomy (Morrow)	1

[a] Three mitral valve reoperations.

CABG = coronary artery bypass grafting.

lation preoperatively, the rhythm was unchanged by the operative approach. In no patient did an atrioventricular conduction defect develop. One 79-year-old patient died in the hospital, but the death was not related to the operative approach.

Comment

Most commonly the left atrium is approached by a median sternotomy and opened by a longitudinal incision between the interatrial groove and the right pulmonary veins [1]. A left-sided anterolateral thoracotomy is mainly used in relation to a closed mitral commissurotomy [2]. In special situations in reoperation on the atrioventricular valves a right anterolateral thoracotomy may still be indicated [3, 4]. Because reconstructive operations of the mitral valve are performed more frequently, optimal exposure of the mitral valvar and subvalvar apparatus is essential, but it can still be poor, especially in the case of a small left atrium. Although several maneuvers to improve exposure with the standard technique have been advocated [5], tears of the left atrial wall due to forced traction can occur, which may be difficult to repair, especially when such a tear extends to the inferior left atrial wall or behind the superior vena cava. Another disadvantage of this approach is that the view of the surgeon toward the mitral valve and especially toward the anterior part of the annulus can be obstructed by bulging of the atrial septum (Fig 4).

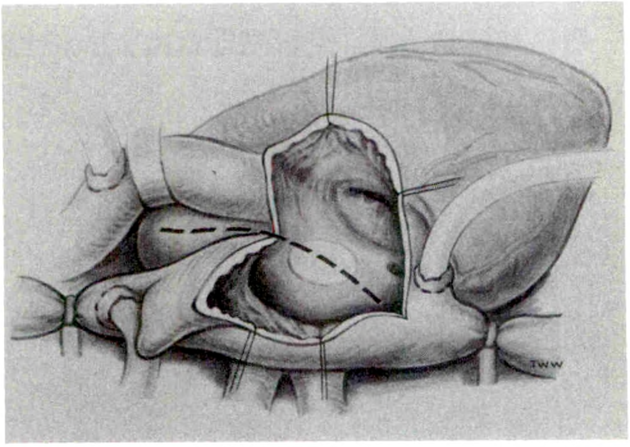

Fig 2. Incision of the interatrial septum and roof of left atrium.

Although the distance to the mitral valve is shorter and vision is better as compared with the standard approach, the superior approach through the roof of the left atrium [6] still gives a limited exposure if this atrium is small.

A combination of the superior approach and the standard approach by mobilization [7] or division of the superior vena cava [8] gives a much broader opening of the left atrium, but the division and reattachment of the superior vena cava is quite cumbersome and may lead to its narrowing or to damage to the sinus node.

If a limited longitudinal incision is made through the interatrial septum after a right thoracotomy [9], or after a median sternotomy [10] in the case of a small left atrium,

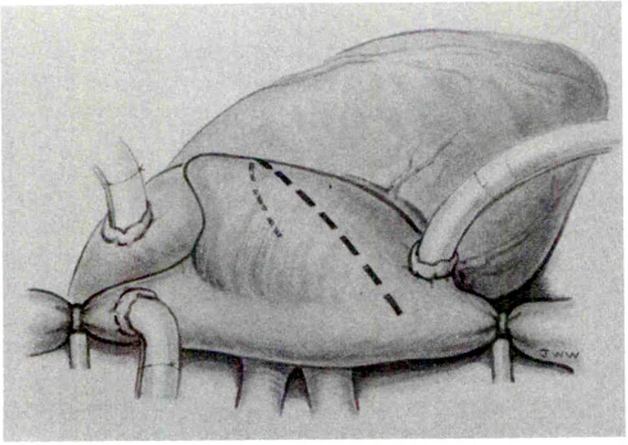

Fig 1. Oblique incision of the right atrial wall.

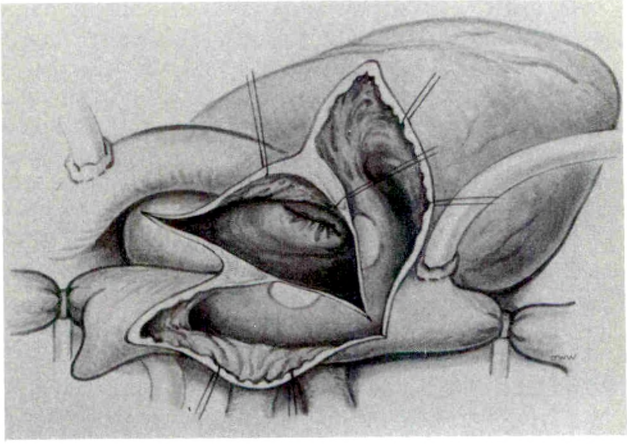

Fig 3. Final exposure of left atrium and mitral valve apparatus.

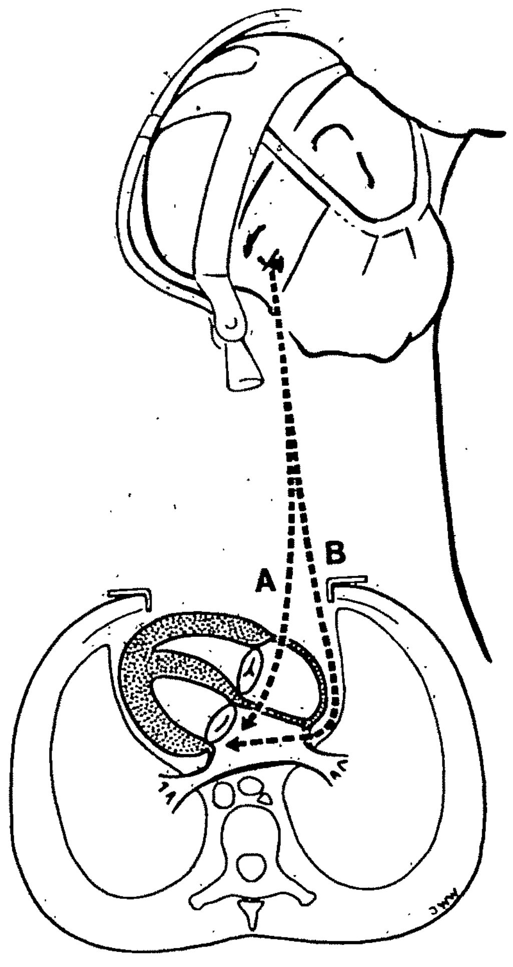

Fig 4. Surgeon's view of the mitral valve: (A) almost nonobstructed view with combined superior-transseptal approach; (B) view obstructed by the interatrial septum with approach through the left atrium only.

the actual opening of the left atrium might be still quite limited and retractors may cause tears to occur near the coronary sinus. A combination of a transverse incision through the interatrial septum and the standard left atrial incision [11, 12] has the possibility of the transverse incision proceeding toward the atrioventricular conduction system.

With the combined superior-transseptal approach to the left atrium as we describe, the surgeon gets very close to all mitral valve structures with an almost unobstructed view (Fig 4), without the need of uncontrollable traction forces. Of course this approach is easy to combine with inspection of or operation on the tricuspid valve.

After the procedure we did not notice any bleeding sequelae, intraatrial shunting, or conduction disturbances. The safety for the conduction system of the limited transatrial septal approach has been confirmed by McGrath and associates [13] recently. We think that this approach to the left atrium provides optimal exposure to the mitral valve, and it is now our approach of choice in all primary and most repeat procedures of isolated or combined mitral valve operations.

We thank J. Wetselaar-Whittaker for her fine hand drawings.

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Late Volume Changes in Retrosternal Colon Bypass

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Esophageal obstruction by malignancy, chemical burns, or other less common entities presents a challenge for the surgeon. Either for esophageal substitution after esophageal resection or as a bypass for the obstructed esophagus, colon interposition is often the best available option. Massive colonic enlargement requiring resection of the interposed dilated colon developed recently in 2 of our patients who had a colon bypass 22 and 10 years earlier, respectively.

(Ann Thorac Surg 1991;51:296–8)

Surgeons have been challenged to restore the capability to eat of patients with esophageal obstruction not amenable to resection and of patients who have undergone an esophageal resection. It was Bircher [1], in 1894, who initially constructed a conduit using a skin tube in a presternal position connecting the cervical esophagus with the stomach. After that, the jejunum, whole stomach, or tubes made from the stomach were used and were positioned in a subcutaneous tunnel. Only in later years were they placed inside the chest. Colon was also initially used for esophageal bypass in a presternal location [2]. In 1952, Montenegro and colleagues [3] reported the use of colon through a transpleural route connecting the cervical esophagus to the stomach. In 1958, Montenegro and Cutait [4] reported a series of 26 patients who were operated on using a transpleural colon interposition with a 19% surgical mortality. Mahoney and Sherman in 1954 [5] reported using the colon in the retrosternal position. The use of this route for colonic bypass grafts represented an advantage over the transpleural route as it is easier to prepare expeditiously the retrosternal space to accommodate the transposed colon. When necessary, the colon can also be positioned in the posterior mediastinum after the esophagus is removed. In all these different positions, the colon proved to be an excellent substitute for the esophagus after esophageal resection or simply for bypassing an esophagus not capable of functioning properly, which is done mostly after chemical burns [6–8].

For many years, it was thought that emptying of the interposed colon was dependent just on gravity [9]. However, recently detailed studies [10] demonstrated that peristaltic activity in the interposed colon is present. But even before these studies, Postlethwait and colleagues [6] had already observed that "surgeons with the greatest experience prefer the isoperistaltic position to prevent gastric reflux."

Reports of long-term survival of patients with colon bypass grafts are not very frequent. In 1975, Wilkins [8] described a patient, operated on by Dr R. H. Sweet, "who has swallowed normally through a colon bypass for seventeen years." We recently had the opportunity to treat 2 of our patients with colon bypass grafts who had been operated on 22 and 10 years before. They had been doing well up to that time, but huge dilatations had developed in the colonic bypass grafts, producing symptoms that required surgical treatment.

Case Reports

Patient 1

A 36-year-old man was admitted to our service in 1980 after he ingested sulfuric acid in a suicide attempt. Two days after admission, he was not yet capable of swallowing his own saliva, and esophagoscopy showed circumferential esophageal burn at 8 cm below the cricopharyngeus. An intraluminal stent was positioned and left in place for 4 weeks. After the stent was removed, dense stricture not responsive to dilation occurred requiring a colon bypass procedure leaving in place the strictured esophagus. An antiperistaltic colon segment was used based on the middle colic artery. Extensive burns of the gastric antrum were also bypassed with a gastrojejunostomy. He did well for almost 8 years when he noticed regurgitation of undigested food that occurred mostly when he went to sleep immediately after a meal. His symptoms could not be managed conservatively, and barium swallows showed an enormously dilated intrathoracic colon with delayed emptying (Fig 1). It was decided to resect the dilated colon through a median sternotomy, being careful to separate the colon away from the sternum by digital dissection before dividing the sternum. After the intestinal wall was freed from the vascular arcades, a segment of colon measuring 28 cm was removed. The distal and proximal retrosternal colonic segments were anastomosed with one layer of running catgut and one layer of interrupted silk suture (Fig 2). The patient did well postoperatively and is doing well 11 months after the coloplasty with no symptoms of regurgitation.

Patient 2

A 17-year-old girl was admitted in 1967 with caustic burns of the esophagus after ingestion of lye. She suffered extensive circumferential burns beginning at 5 cm below

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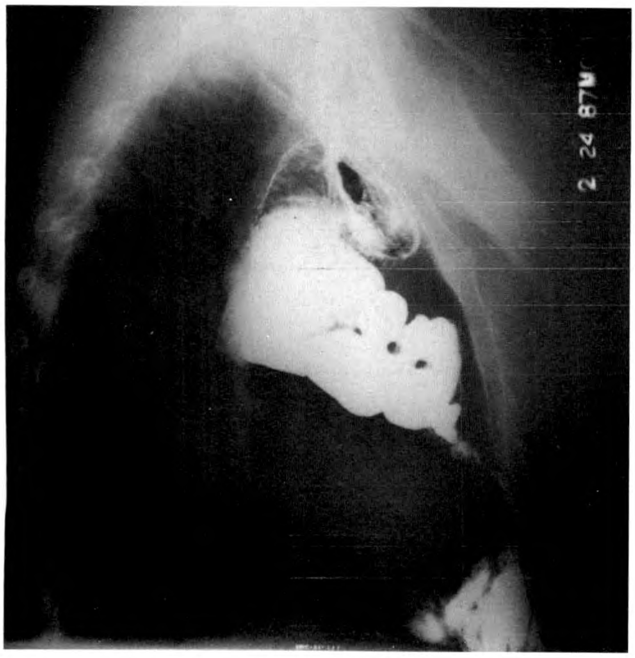

Fig 1. (Patient 1.) Dilated retrosternal colon.

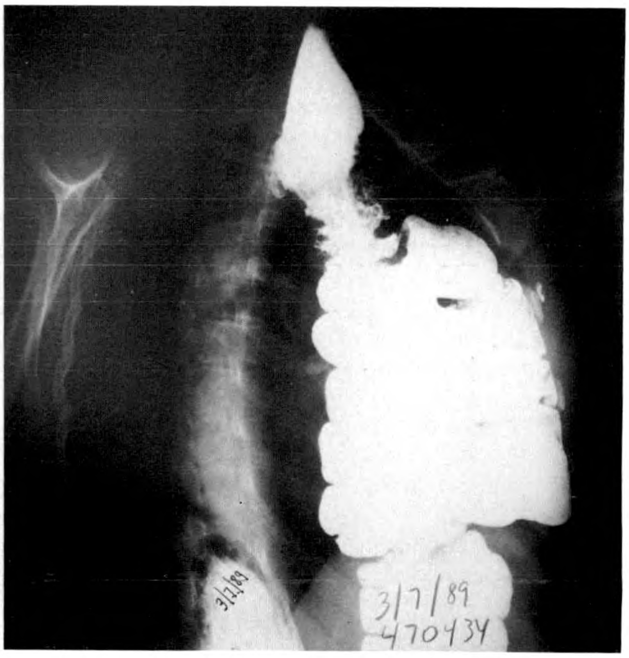

Fig 3. (Patient 2.) Retrosternal colon 22 years after interposition.

the cricopharyngeus. Twelve days after the event, she was started on a regimen of esophageal dilations. After 4 months, it was clear that no progress had been obtained, and a retrosternal colon bypass was performed using a middle colic artery–based colon segment in an antiperistaltic manner. She did well for 22 years; however, in the beginning of 1989, she complained of increasing regurgitation of undigested food that was aggravated by lying down. A barium swallow demonstrated a massive dilatation of the retrosternal colon (Fig 3). A short period of conservative treatment was not successful as her weight went down from 65.8 to 49.5 kg. A transsternal coloplasty was successfully performed by removing a dilated segment of colon followed by end-to-end reconstruction as described for patient 1. The patient did well postoperatively with disappearance of symptoms. One year after operation, her weight was up to 63 kg, and she has continued to do well.

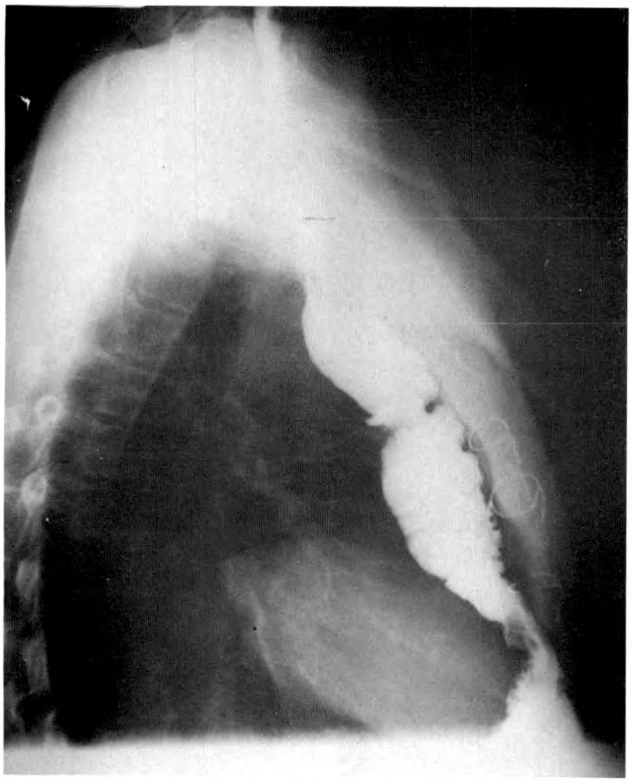

Fig 2. (Patient 1.) After resection of enlarged colon.

Comment

Surgeons familiar with colon bypass grafts recognize the dreadful situation that arises when the mobilized colonic segment is not long enough to bridge the gap between the stomach and the remaining esophagus, usually in the neck. To prevent this occurrence, there is a tendency to harvest a longer segment than necessary. Usually this is recognized during the procedure, and the graft is trimmed to a size sufficient to bridge the gap. If the colonic excess is not detected during the procedure, a postoperative evaluation will determine its presence, and a reduction of its size can be accomplished by resecting the distal excess and redoing the colonic anastomosis to the stomach. In the series published by Wilkins [8], 1 patient with redundant colon had to undergo reoperation. Sterling and associates [11] reported treating 2 patients with distal obstruction of the redundant interposed colon occurring 5 and 10 years, respectively, after the initial procedure. They treated the obstruction by straightening the redundant loops and, in 1 patient, by creating an additional anastomosis between the redundant obstructed loop and the stomach.

In our 2 patients, there was no initial redundant colonic interposition, yet the colon slowly dilated to an extremely large size that interfered with food transport to the stomach, compromising their nourishment owing to unrelenting regurgitation of ingested food.

It is possible that the antiperistaltic position of the colon segment used for the bypass grafts contributed to the dilatation and regurgitation. Through a median sternotomy, the excess volume of colon was safely resected with preservation of proximal and distal blood supplies. We found this technique to be helpful and straightforward in solving this unusual complication.

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Misplaced Caval Filter and Subsequent Pericardial Tamponade

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Use of the Greenfield filter for partial caval interruption is generally accepted as the most reliable mechanical method of pulmonary embolus prophylaxis. However, there have been reports of a variety of (usually nonfatal) complications. We report here the near-fatal complication of acute pericardial tamponade after misplacement of a Greenfield filter. Because of the filter's unusual location, retrieval required cardiopulmonary bypass, profound hyperthermia, and circulatory arrest.

(Ann Thorac Surg 1991;51:299–301)

A 23-year-old man sustained an angiographically proven pulmonary embolus 2 weeks after primary repair of a right femoral vein gunshot wound. Heparin treatment was begun but a second embolus occurred. At an outside institution, a Greenfield filter was inserted through the right internal jugular vein under fluoroscopic guidance. However, the filter was seen to lodge in the right renal vein. Placement of a second device was attempted but resulted in the apparent dislodgement of the filter in the right atrium. No hemodynamic compromise was noted.

The patient was transferred to our institution 1 week later with two misplaced Greenfield filters; several days of persistent low-grade fever; and back, shoulder, and arm pain. Specific technical details of the filter placement procedure were not known to us. Detailed evaluation suggested that the fever was a consequence of recent pulmonary emboli and infarcts. Inferior vena cavogram (Fig 1) and echocardiogram indicated that the filter head extended up into the right atrium. Two of the filter struts, however, appeared anchored in a hepatic vein where it entered the inferior vena cava. The remaining struts appeared to straddle the eustachian valve but did not impinge on the tricuspid valve. There were no arrhythmias, and the fever and back pain subsided over several days. The patient was discharged and instructed to resume oral anticoagulation as filtering efficacy of the device at the caval–atrial junction is not known.

Five days after discharge, the patient was admitted to the same outside hospital with ripping chest and back pain. His prothrombin time was 22 seconds (control = 9.5 to 13 seconds). He was noted to have distended neck veins, a systolic blood pressure of 60 mm Hg with pulsus paradoxus, and a heart rate of 140 beats/min. An emergency cardiac echocardiogram demonstrated probable pericardial tamponade. The patient stabilized after pericardiocentesis of 650 mL of blood. This resulted in a prompt increase in the patient's systolic blood pressure to 140 mm Hg and a decrease in heart rate to 100 beats/min.

The patient was transferred directly to our operating room with a presumptive diagnosis of cardiac perforation with acute pericardial tamponade secondary to a misplaced, intracardiac Greenfield filter. Appropriate large-bore intravenous catheters, a left internal jugular central venous pressure catheter, and a radial artery line were placed with the patient in the semierect position. After rapid sequence induction of anesthesia, a median sternotomy was rapidly performed and a tense pericardium was entered. Large quantities of both old and new blood clots were removed. Two legs of the filter had perforated the right atrium, inferior to the caval–atrial junction. The remainder of the filter could be palpated within the inferior vena cava as far down as the diaphragm. Its location, therefore, precluded simple access to proximal control. In addition, an inferior vena cavogram performed before this admission had indicated that two of the filter legs were probably entrapped in a major hepatic vein.

The patient was placed on cardiopulmonary bypass and core-cooled to 18°C. Maximal cerebral protection was provided by phenobarbital coma (thiopental, 40 mg/kg administered intravenously). The patient's head was packed in ice. The two perforated legs of the filter were amputated outside the right atrium with a wire cutter. Cardiopulmonary bypass was discontinued after a core temperature of 18°C was reached. A low right atriotomy was performed and extended down the anterior surface of the inferior vena cava to the level of the diaphragm. A long curved snap was used to grasp the two legs of the filter caught in the hepatic vein. The struts were dislodged by further advancing them inferiorly down the vena cava. Each of the other filter legs was similarly dislodged, and the entire filter was delivered through the right atriotomy incision. The incision was then closed and cardiopulmonary bypass was reestablished. Total circulatory arrest lasted 10 minutes 38 seconds. The patient was rewarmed

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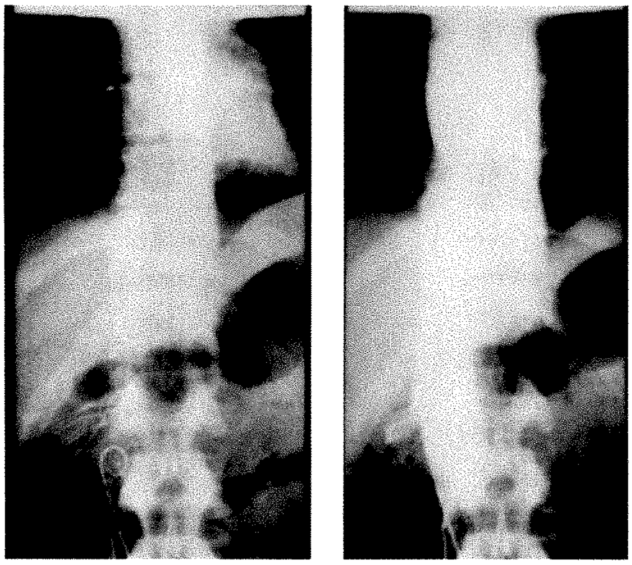

Fig 1. Inferior vena cavogram demonstrating aberrant location of two Greenfield filters.

and the remainder of the operation was completed in the standard fashion.

The patient did extremely well postoperatively and was discharged on the seventh postoperative day.

Comment

Use of the Greenfield filter remains a reasonably safe and extremely effective method of partial caval interruption. The literature is, however, replete with reports documenting filter misplacement. A variety of different complications has been documented [1, 2] with filter misplacement in each of these anatomical locations. Accidental misplacement of the filter in the heart [1, 3] and its migration there [4, 5] have also been reported.

Although filters misplaced in the heart have usually been removed surgically, in 2 patients intracardiac filters were not removed because of surgical risks [5, 6]. These patients experienced no filter-related complications during the ensuing 6 weeks and 18 months, respectively. Furthermore, despite simultaneous anticoagulation therapy, bleeding is a rare complication of Greenfield filters placed in the inferior vena cava [2]. We are unaware of pericardial tamponade complicating filter placement.

This report describes yet another specific catastrophe that, given the widespread use of the Greenfield filter, quite possibly may be seen again. The misplacement of the filter in this patient was such that its legs straddled the eustachian valve at the caval–atrial junction. Two of the legs projecting down the vena cava were fixed at the level of the hepatic veins. The head of the filter was then rhythmically rocked by cardiac contraction. The two legs of the filter found to have perforated the right atrium may have done so at the time of original placement or later as a result of the constant motion of the filter.

The management decisions in this patient were complex and without precedent. Given the unestablished efficacy of the filter in this aberrant location, cautious anticoagulation was continued in this patient as pulmonary embolus prophylaxis. With benefit of hindsight and knowledge of the subsequent events, we have reexamined the initial decision to leave the filter in place. We now believe that the rhythmic motion of the filter in this specific location, causing overt atrial perforation, creates a far more lethal situation than the usually clinically silent inferior vena caval wall perforations occasionally seen with filter placement [7]. Although an incidental perforation of the heart may be a clinically silent event in the patient who was not given anticoagulation therapy, it may represent a far more catastrophic event in a patient being given anticoagulation treatment.

As a result of this case, we recommend that with any filter found to have been misplaced at the level of the right atrium, the possibility of surgical removal must be entertained as soon as its location is confirmed by echocardiography. The clinical combination of intraatrial filter misplacement and anticoagulation may make cardiac perforation and acute pericardial tamponade a rare, but nevertheless more likely, event. Because proximal caval control may be impossible, strong consideration should be given to the use of deep hypothermia and circulatory arrest to aid safe surgical filter removal.

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INVITED COMMENTARY

Misplacement of the Greenfield filter should be a rare occurrence if the guidewire technique is used as recommended, positioning it in the inferior vena cava before the carrier is threaded over it. This is the most effective way of avoiding the orifice of the right renal vein. It does not, however, completely exclude the possibility of dislodgement at the level of the atriocaval junction, where the eustachian valve may prevent the carrier from entering the vena cava. At this point, manipulation of the guidewire may extrude the filter prematurely or some tissue may be forced into the carrier engaging the hooks, whereupon there is no alternative but to leave the filter at that level. If this occurs, and the filter remains upright with the apex in the right atrium, it usually causes no difficulty for the patient; however, it is advisable to insert a second filter at the appropriate level in the vena cava from the femoral vein approach.

In this report by Lahey and associates, the combination of a tilted filter that engaged the atrial wall placing it in constant motion and excessive anticoagulation resulted in bleeding with pericardial tamponade. Lahey and colleagues wisely recognized the problem and promptly relieved the tamponade and extracted the filter under profound hypothermia. The latter approach is appropriate as extraction can be difficult. My colleagues and I [1] have described a technique for recapture of misplaced filters using a guidewire and the jugular inserter, but we recommended it only for filters that interfere with the tricuspid valve or that produce rhythm disturbances.

This is only the second patient of whom I am aware who has had pericardial bleeding in association with filter misplacement. The true incidence of filter misplacement is unknown, but I am often consulted and over the past 6 months, I have been notified of 12 misplacements, 9 at the atriocaval junction and 3 in the superior vena cava, none of which produced problems or required removal. This seems like a substantial number, but there have been more than 60,000 filters inserted since it was introduced.

The next generation of titanium and modified stainless steel filters that await FDA approval will obviate this problem as they are designed to be inserted percutaneously through a sheath that will extend all the way to the level of desired insertion. Therefore, any inadvertent discharge will be into the sheath rather than into the patient. The filter hook has also been modified to achieve fixation without penetration. Until these are available, there would appear to be little risk from filters at the atriocaval junction unless they are tilted and can be observed to move with atrial contraction under fluoroscopy.

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Total Unilateral Lung Gangrene in Hodgkin's Disease: Treatment by Thoracostomy

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Total gangrene of the left lung developed in a 30-year-old male patient with a pulmonary recurrence of Hodgkin's disease after mediastinal irradiation and chemotherapy. Clinically, tension pyopneumothorax and severe septic shock were present. Surgical repair was done by thoracostomy, resecting three ribs. A 2 × 0.5-cm hole in the necrotic wall of the left main bronchus was covered with an intercostal muscle bundle. The necrotic pleural surfaces were treated openly by daily change of dressings. The patient recovered satisfactorily and underwent four further courses of chemotherapy without any complications.

(Ann Thorac Surg 1991;51:302–3)

In patients with neoplasms, a variety of complications requiring thoracic operation may occur. We present the unusual case of total left-sided lung gangrene in a patient with Hodgkin's disease.

In July 1982, nodular sclerosing Hodgkin's disease PS III A_{S+} (mediastinal bulk, abdominal lymph node, and splenic involvement) was diagnosed in a 23-year-old male patient. Splenectomy and subtotal nodal irradiation (mantle and paraaortic field plus splenic pedicle; telecobalt: 43.5 Gy mediastinal dose) were performed, resulting in a complete response in June 1983. By computed tomographic scans, radiation-induced fibrosis in the left middle lung was detected in September 1984, increasing in extent until September 1986.

In June 1989, the computed tomographic scan showed a tumor at the left hilum with a maximum size of 15 × 20 × 20 cm diffusely infiltrating the left lung. Stenosis of both the left upper and lower lobe bronchi, upper lobe atelectasis, and pericardial and pleural effusions were present (Fig 1). Bronchoscopy and biopsy confirmed a relapse of Hodgkin's disease: 1 cm distal to the carina, all visible bronchial walls on the left side were lined with whitish tumor masses.

Fourteen days after induction of chemotherapy (cyclophosphamide, vincristine, procarbazine, and prednisolone) the patient had fever (38°C) and cough with mouthful purulent expectorations. Under antibiotic therapy the fever subsided. Three days later, palsy of the left laryngeal recurrent nerve developed. Another 7 days later, the patient was admitted to our department with severe septic shock, mouthful expectorations of foul-smelling liquid, and an acute left tension pneumothorax requiring emergency thoracostomy in which 4 L of gangreneous fluid mixed with chunks of fleshy material was evacuated. A large bronchopleural fistula allowed only Heimlich's drainage, as any suction immediately resulted in shortness of breath. The lung failed to reexpand. The bacteriological specimen yielded *Veillonella parvula* and *Streptococcus viridans*. Bronchoscopy showed a 0.5 × 2-cm hole in the left main bronchus 1 cm distal to the carina. All visible left-sided bronchial walls were lined with necrotic tissue.

Four days later, with the general condition of the patient sufficiently stabilized by intensive care measures, left thoracotomy was done. The pleural cavity was filled with gangrenous debris. The central, equally gangrenous pulmonary structures were impacted into a necrotic bulk, covering the whole extent of the mediastinal surface. It was not possible to dissect the hilar region. The pulmonary vessels, as far as they could be identified, were thrombosed. The caudal circumference of the left main bronchus had vanished in an area of 0.5 × 2 cm. We did debridement as far as feasible. A large thoracostomy was created, resecting ribs 5 to 7. The bronchial leakage was covered with the help of two intercostal muscle bundles, loosely put into the hole and secured by stay sutures. The pleural cavity was tightly packed with Betadine-soaked dressings. The specimens of debris, pulmonary tissue, and of the mediastinal bulk showed barely discernable alveolar structures with thrombosis of the stromal vessels as well as necrotic remnants of the tumor.

Systemic antibiotic therapy along with intensive care measures was administered. The dressings were changed every day. The patient, who continued to cough up necrotic material for 15 days, improved rapidly, while the computed tomographic scan showed cavities in the gangrenous, residual lung (Fig 2). After 8 weeks, the necroses had separated leaving a homogeneous, fibrotic mass at the mediastinal surface (Fig 3). Further treatment was done on an outpatient basis. A small air leak at the main bronchus closed spontaneously after 3 months. Broncho-

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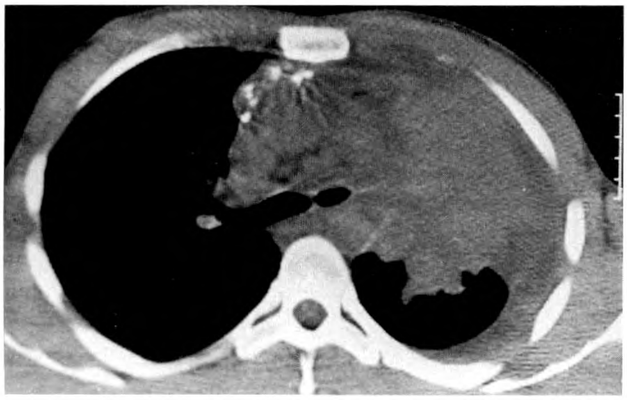

Fig 1. Large, homogeneous mass in the left hemithorax, extending from the mediastinum to the chest wall. The tumor involves both upper and lower lobes with a stenosis of the left bronchial system. A pleural effusion is present.

scopically, the left main bronchus was blandly obliterated, mimicking findings after pneumonectomy. With the pleural cavity showing clean granulation tissue, four further chemotherapy courses (Adriamycin [doxorubin hydrochloride], bleomycin, and vinblastine) have been administered without any complications. The residual pleural cavity will be closed by thoracoplasty in due course.

Comment

The etiological factors of pulmonary gangrene are similar to those of aspiration pneumonitis or of abscess [1]. Any devitalized or undersupplied lung area is at risk for the development of gangrene, a variety of predominantly anaerobic bacteria triggering the process [1, 2].

In our case, an interaction of peculiar factors might have been causative: (1) Mediastinal irradiation had obviously caused some structural—predominantly microvascular and alveolar—damage to the left central pulmonary region as documented by fibrosis. This type of radiation-induced damage is found in up to 20% of patients with Hodgkin's disease [3]. (2) The extensive relapse of Hodgkin's disease on the left side involved the hilar structures of the lung, invading the bronchial walls as shown by bronchoscopy. (3) The response to chemotherapy obviously was dramatic, as no vital tumor was detectable at the time of thoracotomy.

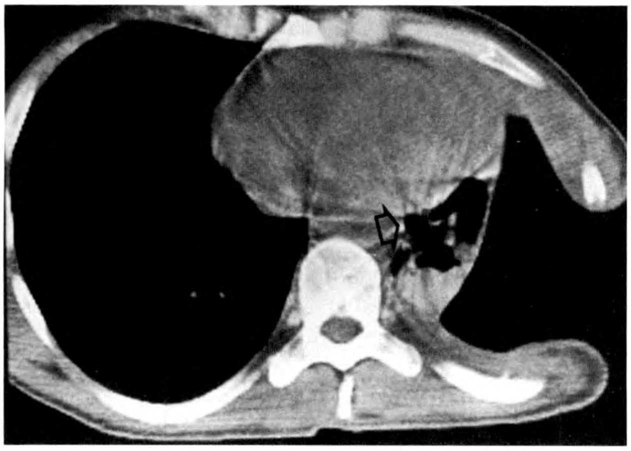

Fig 2. Day 18 after thoracostomy: multiple cavities in the residual, gangreneous left lung, draining into the bronchial system (arrow). The pleural surfaces begin to smooth (the dressings had been removed during the computed tomographic scanning procedure).

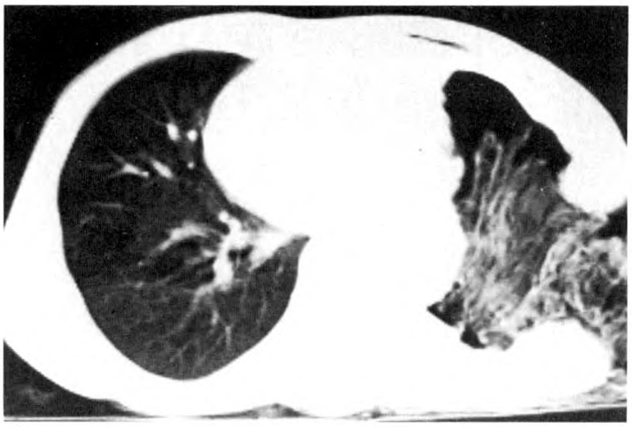

Fig 3. Day 52 after thoracostomy: homogeneous mass at the left mediastinal surface. The intrapleural dressings are in situ.

It could be presumed that chemotherapy-induced tumor necrosis caused acute obliteration of the bronchial arteries, the main supply vessels of the lungs' maintenance circulation [4]. Facultatively pathogeneous bacteria populated the necrosis causing gangrene and secondary stagnation of the pulmonary arterial and venous circulation. Presumably, the detrimental effect was enhanced by the preexistent radiation-induced damage and by the immunosuppression caused by chemotherapy [1, 5].

As resection was not possible, we used the ancient method of thoracostomy, originally used for open abscess drainage in the preantibiotic area [6], which proved to be very effective in supporting a process of spontaneous resolving. The disfiguring effect on the patient has to be weighed against his improved chance of survival.

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Intraoperative Management of Severe Endobronchial Hemorrhage

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Endobronchial hemorrhage due to pulmonary artery perforation by a Swan-Ganz catheter developed during coronary artery bypass grafting while weaning from cardiopulmonary bypass. After reinstitution of cardiopulmonary bypass with pulmonary artery venting, bleeding was localized to the right lower lobe bronchus using fiberoptic bronchoscopy. A Fogarty embolectomy catheter was inflated in the bronchus to tamponade successfully only the right lower lobe. This case illustrates a method of distal bronchial blockade for maximal retention of pulmonary function and avoidance of pulmonary resection.

(Ann Thorac Surg 1991;51:304–7)

Balloon-tipped, flow-directed (Swan-Ganz) catheters are employed commonly for monitoring patients undergoing cardiac surgical procedures. In general, the use of these catheters is accompanied by minimal morbidity. Life-threatening hemorrhagic complications due to pulmonary artery rupture occur at an estimated incidence of one or two per thousand [1, 2] but are associated with a mortality rate greater than 50% [3].

Cardiac surgical procedures that use cardiopulmonary bypass (CPB) and systemic hypothermia may increase the risk of pulmonary artery perforation [4]. Although perforation may occur at the beginning of, during, or at the termination of bypass, it usually does not become apparent until pulmonary blood flow is restored during weaning from CPB. Therapeutic options range from simple reversal of heparinization after weaning from bypass to major pulmonary resection [5, 6]. Endobronchial blockade can be effective, although localization of bleeding in the setting of severe endobronchial hemorrhage is difficult. The facility to resume CPB rapidly, thus effectively interrupting pulmonary blood flow, offers the surgeon the unique opportunity to evaluate and manage pulmonary hemorrhage in a controlled manner.

A 64-year-old man was admitted with the recent onset of angina at rest 2 years after an inferior myocardial infarction. Coronary angiography revealed coronary artery disease involving three vessels and a left ventricular ejection fraction of 0.67. The forced expiratory volume in 1 second was 77% of predicted value and the forced vital capacity was 3.9 L. The electrocardiogram demonstrated normal sinus rhythm and evidence of an old, inferior infarct.

In preparation for elective coronary artery bypass grafting, a Swan-Ganz pulmonary artery catheter was inserted through the right internal jugular vein and advanced to a wedged position with the balloon inflated. The catheter functioned normally, and the pulmonary artery and wedge pressures were normal. After median sternotomy and dissection of the left internal mammary artery, the catheter was retracted a distance of 2 cm. Heparin was administered and CPB was instituted using ascending aortic inflow and Sarns two-stage venous return. A pulmonary artery vent was employed. Coronary artery bypass grafting was performed using systemic hypothermia and cardioplegic arrest. The patient was rewarmed to 37°C and mechanical ventilation was begun before weaning from CPB.

As the patient was being weaned, severe endobronchial hemorrhage (estimated as >100 mL/min) issued from the endotracheal tube. Cardiopulmonary bypass was immediately reinstituted, the Swan-Ganz catheter withdrawn an additional 3 to 4 cm, and the tracheobronchial tree lavaged with normal saline solution. A flexible bronchoscope was inserted through the endotracheal tube, but the bleeding site was difficult to localize because of profuse hemorrhage. Pulmonary vent flow was increased, resulting in the complete cessation of hemorrhage, thus allowing thorough aspiration of the blood-filled tracheobronchial tree. Pulmonary artery vent flow then was decreased gradually until a small but clearly identifiable quantity of blood could be seen emerging from the right lower lobe bronchus.

The patient was extubated and, during direct laryngoscopy, a No. 5 Fogarty embolectomy catheter was inserted in the distal trachea. The fiberoptic bronchoscope was then reintroduced into the trachea through a ventilating right-angle connector on a No. 9 endotracheal tube. Under direct vision, bronchial biopsy forceps were used to maneuver the Fogarty balloon catheter into the orifice of the right lower lobe bronchus. The balloon then was inflated to occlude the bronchus. To test the efficacy of the blockade, pulmonary blood flow was partially restored by occluding the pulmonary artery vent. No bleeding past

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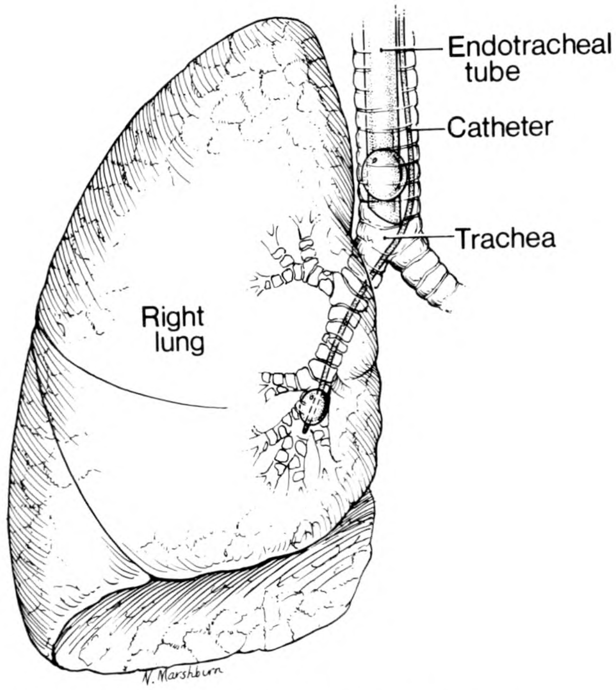

Fig 1. A No. 5 Fogarty embolectomy catheter, guided into the right lower lobe bronchus by flexible bronchoscopy, is fixed in position by the cuff of the endotracheal tube.

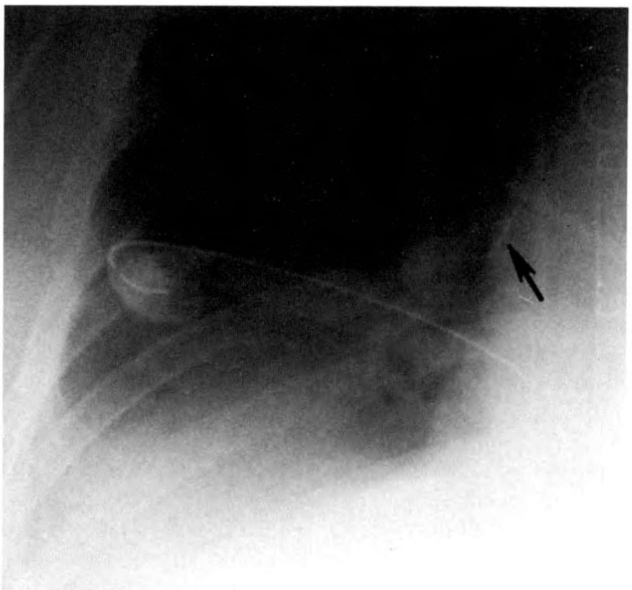

Fig 2. Postoperative chest roentgenogram demonstrating the Fogarty balloon in the right lower lobe bronchus (arrow) *and atelectasis of the right lower lobe.*

the balloon could be identified. The endotracheal tube was then positioned approximately 2 cm above the carina where the cuff was inflated, thus fixing the Fogarty catheter in place (Fig 1). The bronchoscope remained in place after mechanical ventilation was resumed and during weaning from CPB, then was withdrawn when no further bleeding was noted. The surgical procedure was completed without further incident. A postoperative chest roentgenogram in the surgical intensive care unit demonstrated the Fogarty catheter in the right lower lobe bronchus and atelectasis of the right lower lobe (Fig 2).

In the surgical intensive care unit 24 hours after operation, a flexible bronchoscope was reintroduced through the endotracheal tube and the Fogarty balloon was deflated under direct vision. Thrombus was seen beyond the point of balloon occlusion, and there was no active bleeding. The Fogarty catheter was left in place with the balloon deflated for a subsequent 24 hours after which both it and the endotracheal tube were removed. Subsequent reexpansion of the right lower lobe was confirmed by chest roentgenogram (Fig 3). No further pulmonary hemorrhage developed throughout the remainder of the patient's hospitalization and he was discharged home on the 15th postoperative day.

Comment

The first report of pulmonary hemorrhage as a complication of flow-directed pulmonary artery catheterization appeared less than 2 years after its introduction into clinical practice [7]. Risk factors include peripheral catheter location, pulmonary artery hypertension, advanced age, anticoagulation, and hypothermia [4, 8]. More than half the reports of pulmonary artery rupture stem from patients undergoing CPB, perhaps because of hypothermia-induced catheter stiffening and cardiac manipulation [4].

For this reason, it is recommended that before initiation of CPB, the catheter should be withdrawn from 2 to 15 cm [4, 9]. This maneuver is intended to prevent retraction of the deflated lung over a stiffened catheter. Techniques to control the severe hemorrhage of intraoperative pulmonary artery perforation include temporary ligation of the ipsilateral pulmonary artery [10], mechanical ventilation with positive end-expiratory pressure [11], endobronchial blockade techniques [5], and major pulmonary resection [2, 6]. The use of positive end-expiratory pressure is

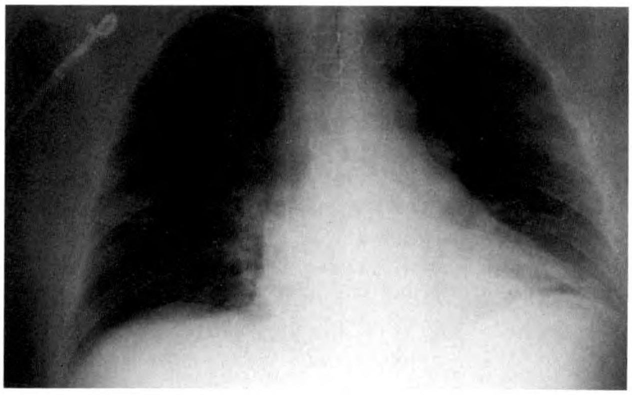

Fig 3. Chest roentgenogram 1 week postoperatively, demonstrating complete reexpansion of the right lower lobe after withdrawal of the Fogarty balloon catheter.

attractive because of its simplicity, but reliance on nonmechanical blockade may not prove adequate to control severe hemorrhage. Mechanical endobronchial blockade techniques are effective when the iatrogenic trauma to the pulmonary artery results primarily in endobronchial rather than intraparenchymal or free intrapleural bleeding. In the emergent situation, tamponade of either the right or left main bronchus can be accomplished rapidly and effectively using a double-lumen endobronchial tube but with the undesirable consequence of severe ventilation-perfusion mismatching.

The technique described in this report of controlling intraoperative endobronchial hemorrhage has several advantages over conventional methods. The employment of the flexible fiberoptic bronchoscope promotes distal visualization and efficient aspiration of blood throughout the tracheobronchial tree. The rate of bleeding is controlled by modulation of pulmonary arterial vent flow. Initially, vent flow is maintained at a high rate until all blood has been aspirated. Subsequently, vent flow is gradually decreased until a small quantity of blood is seen emerging from a single bronchus, which is then occluded with a balloon catheter. Distal placement of endobronchial occluders minimizes the volume of perfused, nonventilated lung and should be expected to have the fewest undesirable effects on pulmonary function. This ability to employ greater selectivity in placement may be especially important in the management of patients with marginal pulmonary reserve.

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INVITED COMMENTARY

Pulmonary artery perforation is an unusual complication of Swan-Ganz catheter placement that has a very high reported mortality when detected in heparinized patients during weaning from cardiopulmonary bypass. Although at meetings I have heard verbal reports of successful management with bronchial occlusion and associated methods to avoid pulmonary resection and maximize retention of pulmonary function, this report by Purut and associates is the first published documentation I have seen of survival after a nonresective approach to this dreaded complication. In contrast, in a case my colleagues and I recently reported [1], good control of endobronchial bleeding was also obtained with Fogarty balloon catheter occlusion of a right lower lobe segmental bronchus. However, we felt impelled to "be conservative" and proceeded to right lower lobectomy. Resection of any portion of the lung through a median sternotomy incision is associated with an inevitable minimum of cardiac compression and hemodynamic compromise, and the risk of bleeding from the pulmonary hilum and lung is certainly increased in the face of compromised coagulation after cardiopulmonary bypass. In addition, air leaks are frequent, increasing the risk of further pulmonary compromise in addition to the loss of the resected lobe. I believe that these factors played a major role in the death of our patient, and I compliment Purut and associates on documenting the effectiveness of a less invasive and more physiological approach.

Leaving the lobe with the Swan-Ganz catheter-perforated pulmonary artery branch in place also has its risks including continued or intermittent low-grade endobronchial bleeding, with soiling of the other lung and massive continuing hemorrhage into the damaged lung or free into the pleural space. However, when all factors are considered, a nonresective approach would now be my first choice whenever bleeding can be controlled. Resolution of the hematoma and potential for recovery of prebypass pulmonary function are frequently observed, as would be expected from the trivial nature of the arterial injury. In our case, as in several previously reported, the pulmonary artery perforation could not be detected by fine sectioning of the arterial branch entering the hematoma.

An unresolved issue is whether or not to pull back the Swan-Ganz catheter from the site of injury. Patient salvage has also been reported by leaving the pulmonary artery catheter in place and gently inflating the Swan-Ganz balloon. A combination of pulmonary artery and endobronchial balloon inflation could conceivably control both vascular inflow to and bronchial outflow from the site of injury.

Although not noted in the present report, the side of the final placement of the Swan-Ganz catheter, which, except in rare cases, is also the side of rupture, can be easily identified by encircling and palpating the right pulmonary artery between the superior vena cava and the aorta. Snaring the appropriate pulmonary artery will also essentially control hemorrhage to allow bronchopulmonary toilet and location of the specific bleeding lobar bronchus. Whether or not removal and replacement of the endotracheal cannula with inflation of its balloon to fix the Fogarty catheter against the tracheal wall is required remains to be demonstrated, but it is certainly superior to the invasiveness of pulmonary resection.

In this paper by Purut and associates, the mortality associated with Swan-Ganz pulmonary artery injury is reported as greater than 50%. However, it should be understood that this is in association with cardiopulmonary bypass and systemic anticoagulation. Pulmonary hematomas are seen on occasion in patients in coronary care units, for example, and are frequently benign and self-limited.

Finally, a little more detail should be provided for prevention. A most important feature is withdrawal of the end of the Swan-Ganz catheter into the distal main pulmonary artery. The recommendation by Purut and associates of a 2- to 15-cm withdrawal is not specific enough. Length of insertion for fixation after wedging should be 40 to 50 cm, depending on the patient's size, with the recognition that sometimes a wedge pressure can only be obtained after redundant curling of the catheter. The decision on how far to draw back should not be left to a range of predetermined distances. Thoracic surgeons will work with anesthesiologists of varying experience and, during all the other details of preparation for cardiopulmonary bypass, a question about the depth of the Swan-Ganz catheter insertion is not out of place. As with most things in medicine, if a little is good a lot is not necessarily better. One group has recommended that the Swan-Ganz catheter be pulled back to only a 30-cm depth of insertion, but inflation of the balloon at this depth will occasionally lead to obstruction of a two-stage right atrial catheter, with emptying of the oxygenator and major risk of air embolus. This has been reported in the literature by Shah and co-workers [2] and experienced once in our center during the use of approximately 6,000 Swan-Ganz catheters during cardiopulmonary bypass. Again I compliment Purut and associates on an important contribution.

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Nephrotic Syndrome Complicating Adenocarcinoma of the Lung With Resolution After Resection

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Nephrotic syndrome is an uncommon complication of lung cancer. We present a case in which adenocarcinoma was complicated by the nephrotic syndrome, which resolved after resection of the cancer.

(Ann Thorac Surg 1991;51:308–9)

Nephrotic syndrome is a well-recognized complication of neoplastic disease. This report describes a case of acute nephrotic syndrome associated with adenocarcinoma of the lung. It is of interest that the proteinuria remitted after resection of the tumor.

A 75-year-old man was admitted with bilateral lower extremity edema and a 13.5-kg weight gain. There was no history of hypertension or other renal disease. He had undergone a coronary bypass operation 8 years previously and had suffered no angina or cardiac problems since the operation. He had a 40-pack-year history of cigarette smoking, but had discontinued smoking 20 years previously.

On physical examination, his blood pressure was 130/85 mm Hg and his weight was 84 kg. There were decreased breath sounds in both lung fields. Ascites and bilateral, pitting pedal edema were present. Laboratory data at admission included normal electrolyte levels and the following values: blood urea nitrogen, 5.0 mmol/L of urea (14 mg/dL); creatinine, 90 μmol/L (1.0 mg/dL); total protein, 65 g/L (6.5 g/dl); albumin, 24 g/L (2.4 g/dL); and cholesterol, 8.82 mmol/L (341 mg/dL). Twenty-four–hour urinary protein excretion was 10.37 g. Serum antinuclear antibody test was negative, serum complement including C3 and C4 were normal, serum protein electrophoresis was normal, and urinary protein electrophoresis showed nonselective proteinuria with no evidence of a urinary paraprotein.

The patient's chest roentgenogram at admission showed a cavitary lesion in the left upper lobe and a nodule in the right lower lobe. His initial treatment included intravenous diuretics. Computed tomographic scan of the chest showed no evidence of enlarged mediastinal lymph nodes, and computed tomography–guided fine-needle aspirations showed granulomas in the right lung nodule and adenocarcinoma in the left upper lobe lesion. The patient underwent left thoracotomy and upper lobectomy with complete resection of the adenocarcinoma (Fig 1). There was no gross evidence of mediastinal lymph node metastasis, and bronchial and mediastinal nodes sampled at operation did not contain metastases. The patient had a transient episode of acute renal failure after operation, which resolved spontaneously. A postoperative adynamic ileus resolved as his weight returned to normal with continuation of his diuresis. He was discharged 17 days after the operation. His weight upon discharge was 76 kg.

One month after operation, follow-up examination showed no peripheral edema and his weight was 69 kg. Twenty-four–hour urinary protein excretion was 216 mg. Renal function tests disclosed the following levels: blood urea nitrogen, 7.1 mmol/L of urea (20 mg/dL); creatinine, 120 μmol/L (1.4 mg/dL); and serum protein, 79 g/L (7.9 g/dL). He has continued to do well with no recurrence of his nephrotic syndrome or of the tumor 6 months after the operation.

Comment

The nephrotic syndrome has been reported as a complication of a variety of malignant diseases including Hodgkin's disease, non-Hodgkin's lymphoma, sarcoma, leukemia, and various carcinomas, of which lung carcinoma is the most common [1, 2]. The nephrotic syndrome in this setting may be the presenting feature of the malignant disease, typically a slow-growing malignancy and thus may precede recognition of the tumor [3], as in this case.

The renal lesion most commonly responsible for the nephrotic syndrome in association with carcinoma is membranous nephropathy [4], the pathologic diagnosis of which includes recognition of immune complexes on the subepithelial surface of the glomerular basement membrane [5]. Tumor-related antigens have been identified in these immune complexes after elution of the antibody [6], and this antibody, in patients with bronchogenic carcinoma, has shown reactivity against tumor extract [7, 8]. Specific evidence of circulating immune complexes is lacking, and it is believed that in-situ formation of immune complexes on the basement membrane is the more likely pathogenesis for this lesion [5].

Although no renal histological data were available in the present case, it is presumed that our patient had membranous nephropathy secondary to adenocarcinoma of the lung with subsequent development of the nephrotic

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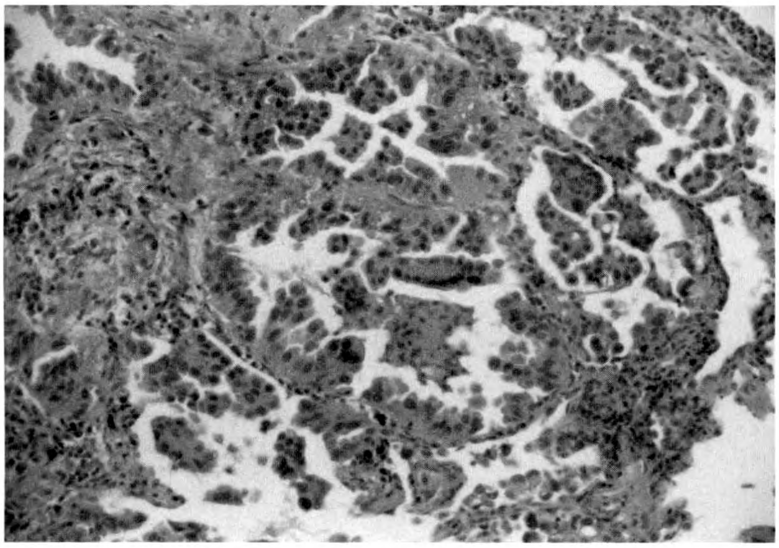

Fig 1. Photomicrograph of the tumor demonstrating adenocarcinoma. (Hematoxylin and eosin; ×20 before 38% reduction.)

syndrome. Furthermore, the postoperative complications that occurred likely are secondary to the nephrotic syndrome or its effects. Transient idiopathic acute renal failure is a common complication of the nephrotic syndrome [9], and the resolution of the postoperative ileus coincident with continued diuresis and return of body weight to normal suggests an origin associated with bowel edema secondary to the edema-forming aspect of the nephrotic syndrome.

The nephrotic syndrome associated with malignancy tends to occur in the older age groups, and is very uncommon in patients aged less than 40 years. It has been recommended that all patients over the age of 50 years with new onset of nephrotic syndrome and membranous nephropathy be screened for a malignant process, unless there is an obvious primary cause for the glomerulopathy [1, 2].

The prognosis for individuals with cancer-related nephropathy relates primarily to the underlying neoplastic process. In patients with lung cancer, the survival is poor [10]. Although tumor resection has been associated with disappearance of the nephrotic syndrome in certain cases [1], one might not expect sudden remission in cases of membranous nephropathy, which tends to be a chronic disease. The resolution of proteinuria 1 month after tumor resection in the present case is therefore somewhat unusual. It should be noted that recurrence of the proteinuria sometimes heralds recurrence of tumor antigen and metastatic disease [11].

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Transesophageal Echocardiography in Acute Aortic Transection

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Confirming the diagnosis of acute transection of the descending aorta can be problematic. Unnecessary patient movement and time delay are often associated with conventional investigations. We describe a patient in whom such an injury was clearly and quickly defined at the bedside by transesophageal echocardiography.

(Ann Thorac Surg 1991;51:310–1)

Some people survive acute aortic transection and are able to reach the hospital because of pleural or adventitial containment of a mediastinal hematoma. Many of these patients, invariably casualties of high-speed decelerating accidents, have multiple injuries and are often in hypovolemic shock. In the past, aortography [1] has been the gold standard for confirming such a diagnosis, whereas more recently computed tomography (CT) [2] has played a role. The limitations with both of these investigations are that they involve inevitable delays and require the patient, often ventilated, to be transported within the hospital to the radiology or catheterization laboratory when in unstable condition. Of late, we have increasingly used transesophageal echocardiography (TEE) [3–5] for the detection of aortic dissection and other aortic conditions and were particularly impressed with its usefulness in diagnosing a recent case of acute aortic transection. The investigation was carried out at the bedside in the intensive care unit on a ventilated patient within minutes of admission and was followed by immediate surgical treatment.

A 22-year-old motorcyclist involved in an automobile collision was admitted to a peripheral hospital in a shocked state. Initial assessment showed multiple injuries including fractures of both hips, pelvis, right femur, and left radius; a distended abdomen; and a widened mediastinum on chest roentgenogram (Fig 1). The patient was transferred to our hospital by helicopter as having a possible aortic disruption. On arrival the patient, intubated and hand-ventilated, was alive but had no recordable blood pressure. Bilateral carotid pulsations but no limb pulses were present. Considerable abdominal swelling suggested liver or splenic rupture. The patient was mechanically ventilated, and rapid intravenous transfusion, including emergency blood transfusion, restored pulse and blood pressure (systolic, 100 mm Hg) in both upper limbs. No femoral pulses were palpable, however, although Doppler studies showed a faint pulse signal present over both groins. Immediate TEE was performed at the bedside in the intensive care unit using a 5-MHz phased array transesophageal transducer (HP 21362A; Hewlett Packard, Andover, MA). While imaging 30 cm from the incisor teeth, an aortic tear was clearly demonstrated just distal to the origin of the left subclavian artery (Fig 2). A freely mobile flap was seen over a short length of aorta. The highly mobile nature of the flap, whose edge had a free discontinuity within the central aortic stream, was different from the more fixed double-lumen or spiral appearance seen in aortic dissection (Fig 3). The site and localized nature of the process were highly suggestive of aortic transection. Imaging the heart showed no pericardial fluid or cardiac injury. The study was performed without complication and took 10 minutes. A diagnosis of a contained aortic transection was made. The patient was brought to the operating room where, allowing for the relative stability of his then 4-hour-old transection and the likelihood of dying of abdominal hemorrhage, laparotomy preceded thoracotomy.

Abdominal exploration showed large volumes of free blood, extensive retroperitoneal and pelvic hematomas, ruptured mesenteric vessels, and devitalized lower ileum and proximal ascending colon. A distal ileocolectomy was necessary.

After laparotomy, femoral bypass was considered, but extensive swelling in the area of his hip fractures on both sides negated this. A high left-sided posterolateral thoracotomy showed a large hematoma over the aortic arch and a proximal descending aorta with distal extension along the line of the descending aorta. The process was not ruptured but some blood was present in the pleural cavity. Careful dissection defined the proximal and distal aspects of the aorta, which were clamped together with the left subclavian artery. A longitudinal incision was made into the hematoma, and a complete aortic transection was immediately apparent. The retracted edges of the aorta were 8.0 cm apart. The edges were cleanly divided and required minimal trimming before insertion of a 20-mm woven low-porosity Dacron tube graft sewn into position with continuous 3-0 Prolene suture (Ethicon, Somerville, NJ) during a cross-clamp period of 24 minutes. After the chest was closed over drainage and temporary traction was erected for both hip fractures, the patient was returned to the intensive care unit.

His subsequent progress was that of hemodynamic

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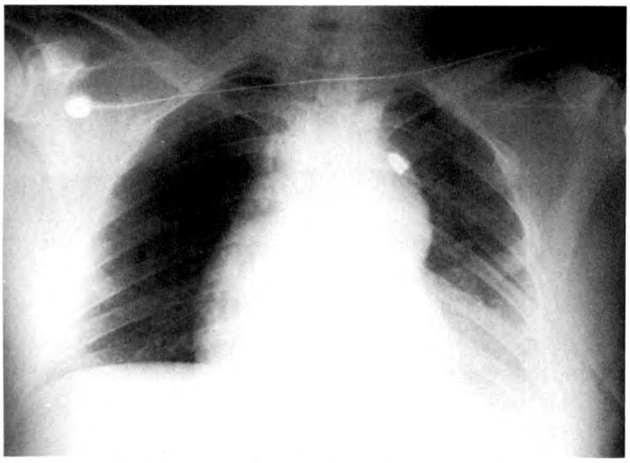

Fig 1. Chest roentgenogram from referring hospital showing widened mediastinum.

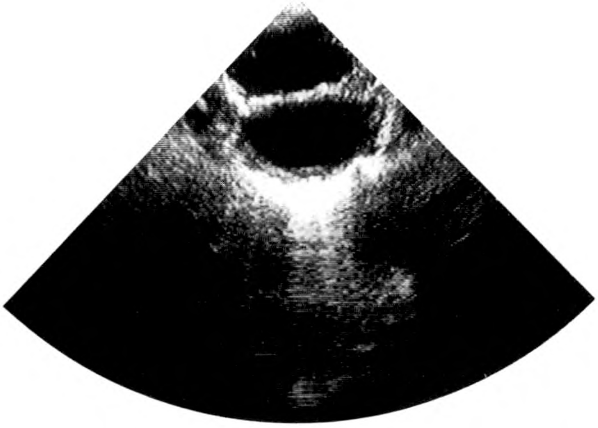

Fig 3. Transesophageal echocardiography of a type B acute aortic dissection from another patient for comparison shows a fixed double-lumen arrangement.

stability, recovery of consciousness, and the ability to move both lower limbs. Unfortunately during a long period of ventilatory support, hepatorenal dysfunction developed, and eventually he died of hepatic coma on the 43rd postoperative day.

Comment

Acute aortic transection, uncommon and usually lethal, occasionally is seen in the emergency room [6]. Much time can be wasted with unnecessary investigations in such a critically injured patient. In this particular patient, TEE gave a rapid definitive diagnosis. Of late, we have been impressed with the use of TEE in the diagnosis and follow-up of other aortic conditions and have increasingly used it with satisfaction in aortic dissection, root abscess, and coarctation. High-quality images are obtained owing to the proximity of the probe to the aorta and to the use of high-frequency transducers. Complications are rare in patients with acute aortic disease [4]. In this case, the quality of the images equalled if not bettered those obtainable from computed tomographic scan and made aortography, which can be hazardous in such a patient, appear irrelevant. On the basis of our experience with TEE, as reinforced by this case, we plan to use it as the next investigation after chest roentgenogram in future cases of likely aortic injury. We anticipate TEE will become the test of choice for the definitive diagnosis of acute aortic transection.

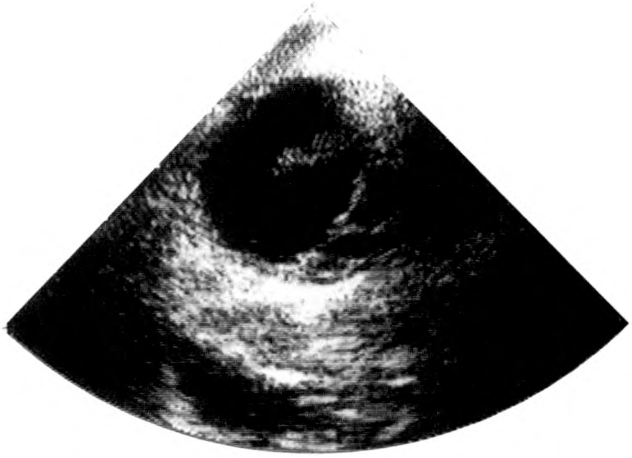

Fig 2. Transesophageal echocardiography of descending aortic transection. A thick and highly mobile flap is best appreciated on real time scanning.

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Aortic Atresia With Normal Left Ventricle: One-Stage Repair in Early Infancy

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Successful one-stage repair of aortic atresia with a left ventricle was performed in a 6-week-old infant using a new technique. After patch enhancement of the hypoplastic aortic arch, the transected proximal pulmonary artery was directly anastomosed to the aortic arch. An intraventricular baffle established continuity between the left ventricle and neoaortic valve, and a homograft conduit was inserted between the right ventricle and pulmonary artery bifurcation.

(Ann Thorac Surg 1991;51:312–4)

Aortic atresia or hypoplasia in the setting of hypoplastic left heart syndrome is a rare malformation with high mortality. Surgical treatment usually requires staged correction [1, 2]. In the presence of a ventricular septal defect with two adequate-sized ventricles and normal atrioventricular valves, a staged biventricular repair has been possible [3, 4], and more recently, a single-stage repair has been described [5]. We describe a modification of the one-stage surgical repair of this complex lesion.

A 2.7-kg term male infant was seen on the second day of life with signs of cardiac failure and mild cyanosis. At initial cardiological assessment, an echocardiogram was performed that demonstrated two atria and two ventricles with concordant atrioventricular and ventriculoarterial connections. There was severe aortic valve and ascending aortic hypoplasia up to the level of the right brachiocephalic trunk, and a discrete distal coarctation. The pulmonary trunk was dilated, and a patent duct could be seen communicating with the aortic arch distal to the coarctation. The left ventricle was of normal dimension, and there was a large perimembranous ventricular septal defect. Initial Doppler echocardiography showed antegrade flow across the aortic valve. Cardiac catheterization performed 24 hours later confirmed the echocardiographic findings. The ascending aorta could not be entered antegradely or retrogradely, and a right ventricular angiogram showed retrograde filling of the ascending aorta through the ductus arteriosus. Ductal patency was maintained with a prostaglandin E infusion. The infant was referred in a stable condition, with a view to performing a Norwood-type procedure. However, ductal patency allowed normal thriving and a more extensive consideration of the surgical therapy. In the presence of an adequate-sized left ventricle and normal atrioventricular valves, it was decided to attempt a biventricular repair.

An operation was performed when the infant was 6 weeks of age and weighed 3.4 kg. Intraoperative echocardiography performed before institution of cardiopulmonary bypass confirmed the findings of the previous investigations, but also showed an absence of antegrade ascending aortic flow (functional aortic atresia). Chordae from the septal leaflet of the tricuspid valve were also demonstrated to cross the ventricular septal defect and were attached to a prominent septal papillary muscle at the lower edge of the defect, which appeared unrestrictive.

The essential steps of the following surgical correction are represented in Figure 1. Cardiopulmonary bypass was instituted with bicaval cannulation and with the arterial cannula in the pulmonary artery. During cooling, the aorta was dissected from the pulmonary artery, and the ductus was identified. At 18°C rectal temperature, the circulation was arrested. The ascending aorta was transversely cut proximal to the right brachiocephalic trunk, and cardioplegia was administered. The arterial duct was cut, and all ductal tissue was removed. The pulmonary artery was cut just proximal to the bifurcation. The aortic arch was then longitudinally opened along the inner curve up to the proximal portion of the descending aorta distal to the coarctation shelf. The aortic arch was reconstructed with a homograft patch, and the main pulmonary artery was anastomosed to the reconstructed arch. The proximal atretic aorta containing the coronary arteries was anastomosed end to side on the right lateral aspect of the neoaorta. After 60 minutes of circulatory arrest, the neoaorta was clamped and cardioplegic solution was injected into the neoaortic root, while circulation was started to rewarm to 24°C rectal temperature. At this stage, the ventricular septal defect was enlarged anterosuperiorly by resection of the infundibular septum. The left ventricle was baffled to the neoaorta with a Gore-Tex prosthetic patch through a longitudinal right ventriculotomy. This procedure necessitated partial detachment of the tricuspid septal papillary muscle and refixation on the baffle. A cryopreserved aortic homograft (diameter, 12 mm) was anastomosed proximally to the right ventriculotomy and distally to the pulmonary artery bifurcation.

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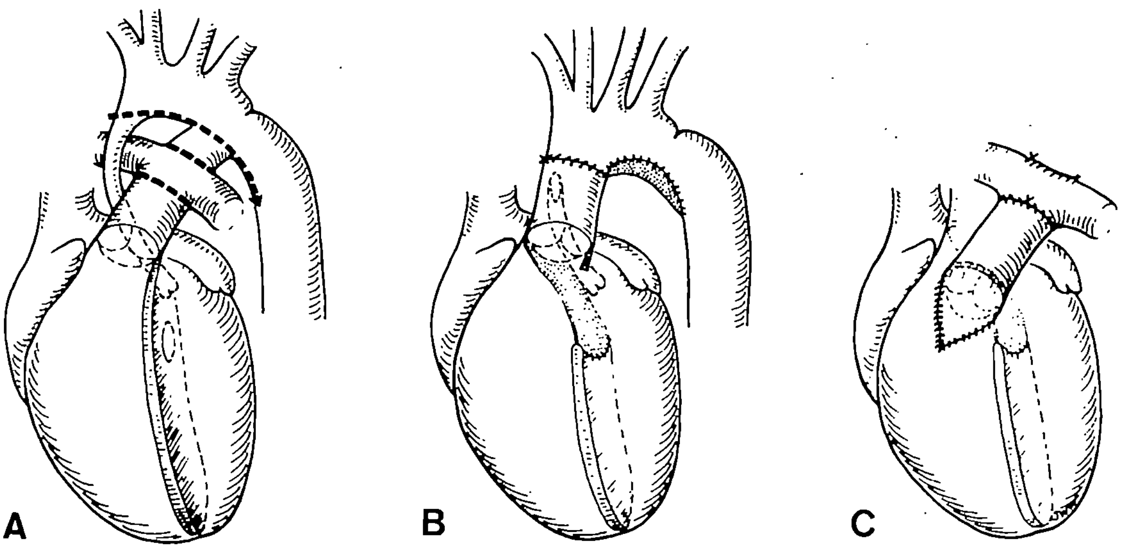

Fig 1. Schematic representation of the surgical procedure in the described case. (A) Incisions are represented by the dotted lines. *The atretic ascending aorta is cut at the base of the right brachiocephalic artery. The arterial duct is cut, and all ductal tissue is removed. From the opening of the cut atretic aorta, the inner curve of the aortic arch is longitudinally opened past the coarctation shelf into the descending aorta. The main pulmonary artery is cut proximal to the pulmonary bifurcation. (B) Reconstruction of the continuity from left ventricle to neoaorta. The main pulmonary artery is anastomosed to the proximal part of the aortic arch. The remaining defect in the inner curve of the arch and descending aorta is reconstructed with an ample homograft patch* (shaded area). *The ascending aorta is anastomosed end-to-side to the neoaorta. The outflow septum is resected, and the left ventricle is baffled to the neoaorta. (C) Reconstruction of the continuity from right ventricle to pulmonary artery. The pulmonary ductal end is oversewn. A homograft is anastomosed between the right ventricle and the pulmonary bifurcation.*

After another 90 minutes, the aorta was declamped and cardiopulmonary bypass and operation ended in the usual way, with standard dosages of intravenous dopamine and nitroglycerin infusions.

Intraoperative epicardial echocardiography performed after the patient came off cardiopulmonary bypass confirmed a satisfactory repair. There were good biventricular function, unobstructed flow from the left ventricle through the pulmonary valve into the neoaorta, and no evidence of residual coarctation. Low-velocity retrograde flow to the aortic root and sinuses could also be shown both by pulsed Doppler echocardiography and color-flow imaging. Laminar flow within the right ventricle to pulmonary homograft was also documented, ruling out any pulmonary outflow obstruction. There was no evidence of mitral or tricuspid regurgitation, or any residual interventricular shunt. The patient was extubated on the third day after operation. Further recovery was uneventful and on the 15th day after operation, the patient left the hospital in good condition. A second echocardiography performed before hospital discharge confirmed the postbypass echocardiographic findings, but also showed a hitherto unsuspected small trabecular ventricular septal defect.

Comment

Aortic atresia forms part of the spectrum of the hypoplastic left heart syndrome. The usual surgical option is to perform a staged univentricular repair using the morphological right ventricle as the systemic ventricle [1, 2]. In approximately 5% of patients with aortic atresia, the left ventricle and mitral valve are adequately developed [6], making it possible to perform a biventricular type of surgical repair and use the left ventricle as the systemic ventricle. Single-stage repair of the defect in the neonatal period is then feasible, as a low pulmonary vascular resistance is not a prerequisite for correction. Austin and colleagues [5] recently reported their experience with single-stage repair of the defect using a nonvalved segment of aortic homograft to establish continuity between the transected proximal pulmonary artery and the aortic arch, in addition to a valved homograft from the right ventricle to the pulmonary artery bifurcation. As pointed out by them, one of the potential problems with this type of repair is the requirement for subsequent replacement of both homograft conduits. In contrast, we used homograft patch augmentation of the aorta, thereby preserving the capacity for the vessel to increase in dimension with age. Additional surgical procedures may be required in the future (right ventricle to pulmonary artery conduit replacement) but should carry fewer risks in the older patient.

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The drawings were skillfully prepared by Mrs Wetselaar-Whittaker from the Department of Anatomy and Embryology, University of Leiden, the Netherlands.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 16, 1992. The closing date for registration is August 1, 1991.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Intraoperative Echocardiography of a Dislodged Björk-Shiley Mitral Valve Disc

Minoru Tanaka, MD, Toshio Abe, MD, Eiji Takeuchi, MD, Takashi Watanabe, MD, and Shuji Tamaki, MD

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The successful management of a patient who suffered an outlet strut fracture of a Björk-Shiley 60-degree convexoconcave mitral valve prosthesis is reported. Emergency operation was life-saving. Preoperative echocardiography assisted in making a prompt diagnosis, and intraoperative echocardiography allowed the detection and removal of the dislodged disc from the left ventricle at the time of the operation. The role of intraoperative echocardiography in the diagnosis of prosthetic strut fracture is emphasized.

(Ann Thorac Surg 1991;51:315–6)

Fracture of the outlet strut of the Björk-Shiley mitral valve prosthesis is a life-threatening complication. A case in which a patient survived emergency mitral valve replacement for outlet strut fracture of a Björk-Shiley 60-degree convexoconcave mitral valve and in which the escaped disc was located and removed successfully with the help of intraoperative echocardiography is reported.

A 42-year-old woman underwent mitral valve replacement with a 29-mm 60-degree convexoconcave valve in January 1981. The postoperative course was uneventful. On December 28, 1988, she was taken to our emergency room with severe dyspnea. Cardiac arrest developed on her arrival, but cardiopulmonary resuscitation was successful. The patient was intubated and mechanically ventilated. The blood pressure was 60 mm Hg systolic, and the heart rate was 160 beats/min. A chest roentgenogram was taken. While we were waiting for the film to be developed, emergency echocardiography was performed that suggested dysfunction of the mitral valve prosthesis. The patient was taken immediately to the operating room where cardiopulmonary bypass was established through the femoral approach.

The chest roentgenogram showed a broken strut and a dislodged disc in the superior mediastinum (Fig 1). The broken strut was detected by palpation in the brachiocephalic artery, and the dislodged disc, in the transverse aortic arch. We decided to remove the fragments after mitral valve replacement. Before the heart was incised, the site of the arterial cannula was changed from the femoral artery to the ascending aorta as the diameter of the femoral artery was very small. The aorta was cross-clamped, and the left atrium was opened. The outlet strut and disc of the mitral valve prosthesis were missing. The prosthetic mitral valve ring was removed and replaced with a Björk-Shiley Monostrut prosthetic valve. The aortic cross-clamp was released, and the heart resumed beating. While cardiopulmonary bypass was maintained, the broken strut was removed through a small incision in the brachiocephalic artery, which required an occlusion time of 6 minutes. Shortly thereafter, we tried to remove the dislodged disc from the aortic arch. However, the disc could no longer be palpated. An intraoperative chest roentgenogram taken just after the removal of the strut showed that the disc was located to the left of the tenth thoracic vertebra. We assumed that the disc had migrated

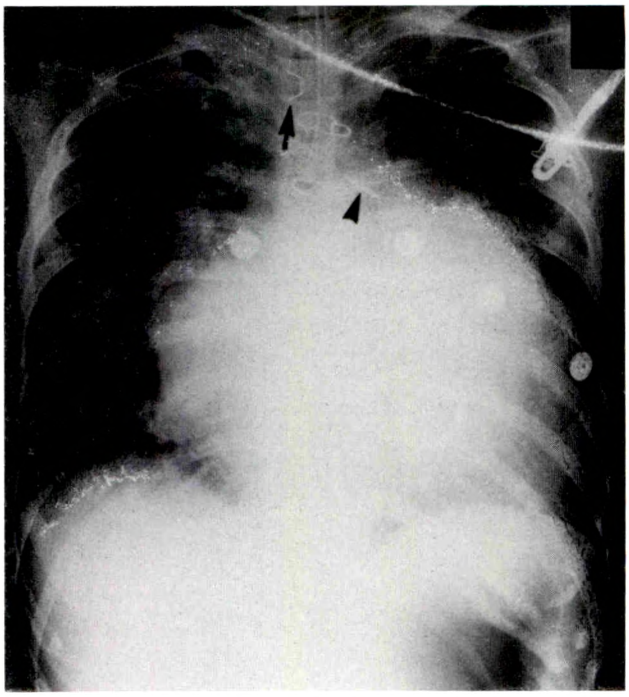

Fig 1. Chest roentgenogram on admission. The ruptured outlet strut (arrow) *and the dislodged disc* (arrowhead) *can be seen in the superior mediastinum.*

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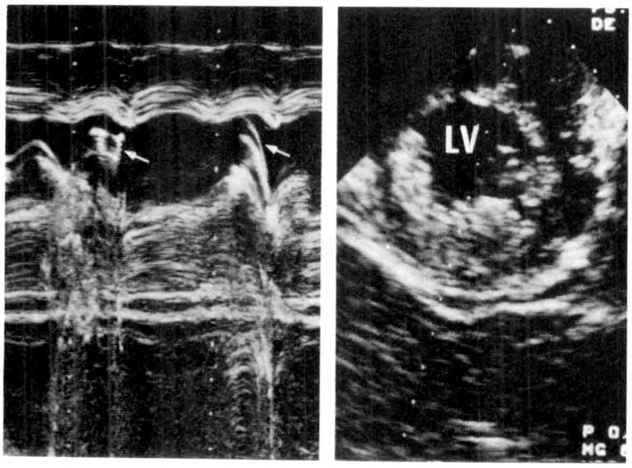

Fig 2. Intraoperative epicardial two-dimensional echocardiogram in the short-axis view of the left ventricle (right) *and its M-mode echocardiogram* (left) *show an echo-dense object* (arrows) *in the left ventricle* (LV), *the movement of which is irregular and asynchronous with the cardiac motion.*

and was lodged in the descending thoracic aorta, but the disc could not be palpated in the descending thoracic aorta, even through a left thoracotomy. Confronted with this situation, we performed intraoperative echocardiography. It showed an echo-dense object moving in and about the left ventricle (Fig 2). The disc was assumed to have somehow migrated retrogradely from the aortic arch into the left ventricle. The aorta was cross-clamped again for 12 minutes, and the disc was removed through the aortic incision. The postoperative course was uneventful.

Comment

Since its introduction in 1969, the Björk-Shiley valve has undergone several modifications. In 1976, the 60-degree convexoconcave prosthetic valve was designed and introduced for general use to improve hemodynamics and to reduce thromboembolic complications. However, it had weld failure of the outlet strut, predominantly in the 29-, 31-, and 33-mm mitral valves, which were withdrawn from the market in 1985 [1]. Although the only hope for survival in patients with strut fracture is early recognition and prompt surgical intervention, the patients often are too ill to survive operation. As the disc was fitted with a radiopaque marker in 1975, chest roentgenography has been the investigative procedure of choice in most patients [2]. In our patient, the disc and strut were visible on the chest roentgenogram. However, severe pulmonary edema, which usually develops in these patients, often prevents a correct interpretation [3]. In such situations, echocardiography provides an alternative means of rapid diagnosis. The preoperative echocardiographic study in this patient showed the absence of disc motion, which led us to perform emergency operation. Dubernet and associates [4] have reported 2 patients who survived and were well without the removal of the dislodged disc. Nevertheless, we think that removal at some point is mandatory, given the existence of potential problems such as erosion, infection, or thrombosis at the site of lodgment. Concomitant disc removal and mitral valve replacement was possible because of intraoperative echocardiography. Echocardiography is not only a useful tool in evaluating mechanical prosthetic valve failure [5, 6], but, intraoperatively, it can provide information important for the surgical management of patients with prosthetic valve failure.

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Delayed Death From Aortic Root Trauma

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A 40-year-old man suffered blunt chest trauma, had a myocardial infarct 58 days later, and died unexpectedly 19 days after that. Autopsy showed partial avulsion of a small branch of the right coronary artery with thrombus extending into the right coronary sinus of Valsalva occluding the right coronary artery and causing a myocardial infarct. Death was caused by a thromboembolus arising from the aortic root thrombus and occluding the left main coronary artery. The case is unusual in that the major consequences of the aortic root trauma were delayed, and death resulted from occlusion of both coronary arteries.

(Ann Thorac Surg 1991;51:317–9)

It is well recognized that blunt trauma to the anterior chest may give rise to aortic injuries [1–4]. Such injuries usually either cause death at the scene, require prompt surgical intervention, or lead to the development of delayed complications. We have observed a rare case in which chest trauma resulted in an aortic sinus of Valsalva mural thrombus that lead to death by thrombotic occlusion of the right coronary artery, followed by thromboembolic occlusion of the left main coronary artery.

A 40-year-old man was in general good health until the truck he was driving was struck from behind, and he was thrown against the steering wheel, then back against the seat, and then against the steering wheel again. He was briefly unconscious and without visible signs of injury. Subsequently he complained of visual disturbances in the right eye, but the exact nature of the eye problem could not be determined. Fifty-eight days later he suffered an inferior myocardial infarction. A catheterization study 10 days later showed total occlusion of the right coronary artery and minimal changes in the left anterior descending coronary artery. His chest roentgenogram was normal. Nineteen days after the infarct and 77 days after the episode of trauma, he collapsed while at dinner and could not be resuscitated.

The major findings at autopsy were in the 415-g heart. In the right coronary sinus of Valsalva, an organizing thrombus was attached to the aortic intima adjacent to and extending into the right coronary artery ostium (Fig 1). The proximal right coronary artery was totally occluded by thrombus, and in the inferior-basilar wall of the left ventricle, in the distribution of the right coronary artery, was a healing myocardial infarct that, on histological examination, was consistent with the 19-day clinical age of the infarct. The left main coronary artery was occluded by a recent thromboembolus that was not attached to the wall of the artery. The myocardium in the distribution of the left coronary artery did not show any gross or histological changes of ischemic injury as a consequence of the very short interval between embolization of the left main coronary artery and death. The right and left coronary arteries were otherwise essentially normal and free of atherosclerotic disease.

The serial histological sections of the thrombus on the intima of the right coronary sinus of Valsalva showed that the thrombus had arisen from a region of partial avulsion of a small branch of the right coronary artery. This artery arose from the right coronary artery just as it passed through the aortic wall. The small artery then ran to the left toward the pulmonary trunk but remained in the adventitia of the aorta. The injury to the vessel was followed by thrombosis of the vessel and by progressive extension of the thrombus into the aortic sinus of Valsalva. Histological examination showed that the thrombus occluding this artery arose at the point where its media and intima had been torn, just distal to the origin of the artery (Fig 2). This part of the organizing thrombus was histologically the oldest found and entirely compatible with an age corresponding to the interval since the accident, namely 77 days. The thrombus that occluded the right coronary artery was continuous with that just described but was not as old, as noted above. The superficial layers of thrombus were of even more recent age and resembled the thromboembolus in the left main coronary artery.

Comment

The clinical information and pathological observations in this patient show clearly that partial avulsion of a small branch of the proximal right coronary artery immediately

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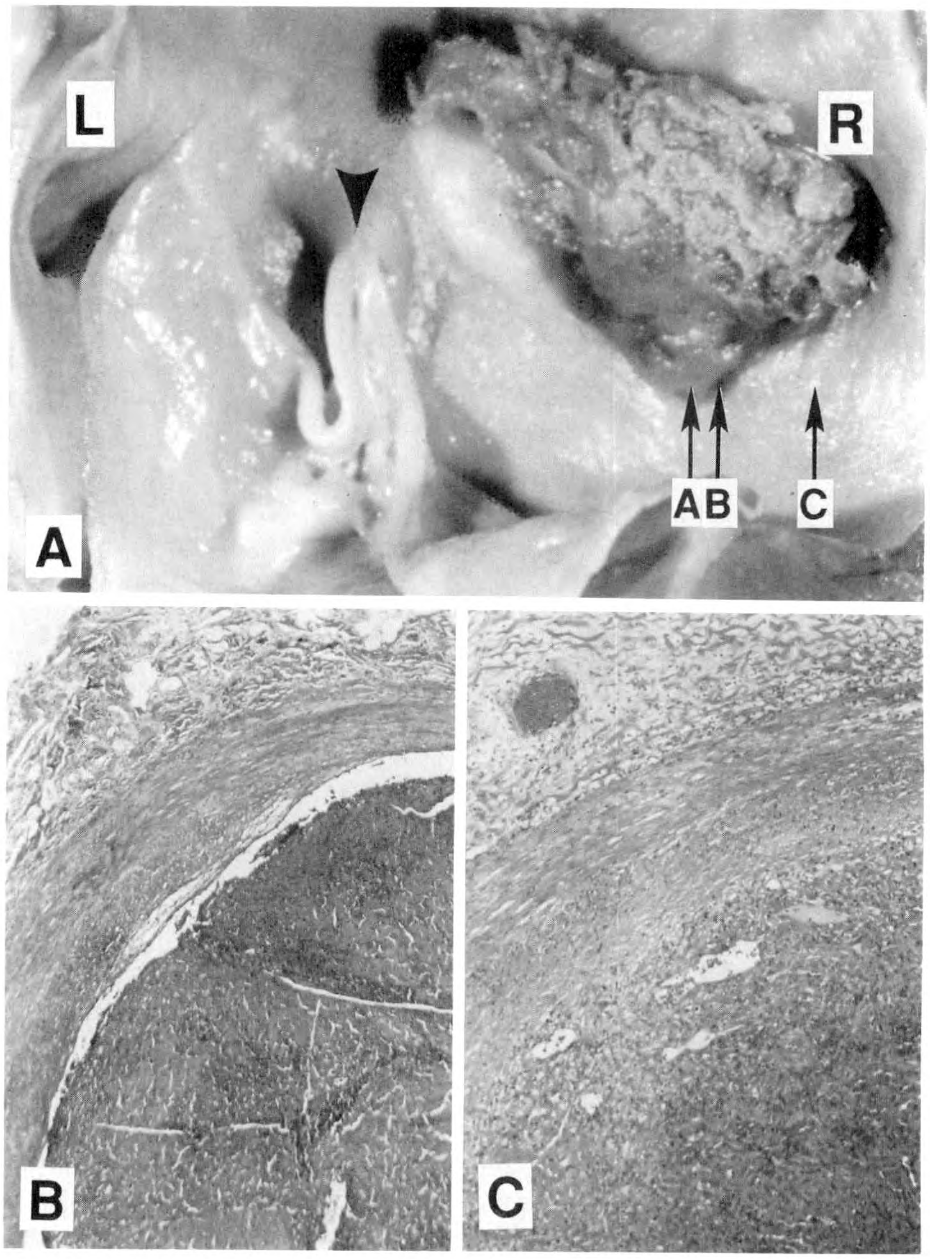

Fig 1. (A) Aortic root showing thrombus in the right coronary sinus of Valsalva. The thrombus fills the right (R) *coronary artery ostium and extends to the left above the commissure (*arrowhead*) between the left and right coronary sinuses of Valsalva. The arrows indicate the plane of the photomicrographs in Figure 2.* (L = *left coronary artery ostium.) (B) Fresh thromboembolus occluding the left main coronary artery. (C) Organizing thrombus occludes the proximal right coronary artery. (B and C: hematoxylin and eosin, ×70 before 16% reduction.)*

adjacent to the aortic wall occurred as a result of a deceleration injury to the aortic root. The aortic root is the first portion of the ascending aorta from the annulus fibrosus to 2 cm superior to the coronary artery ostia [5]. The injury to the vessel was followed by thrombosis of the vessel with propagation of the thrombus into the right aortic sinus of Valsalva. The thrombus extended to occlude the right coronary artery and caused an inferior myocardial infarct. Still later, a thromboembolus that arose from the aortic mural thrombus entered and occluded the left main coronary artery, and death occurred from the resulting cessation of blood flow to the heart.

There are a number of reports of blunt injuries to the anterior chest that have produced immediate death or have required rapid surgical intervention if the patient is to survive. In another group, delayed complications may develop. The present case is unusual in that although death may be ascribed to blunt chest trauma, the interval from the injury to death was 2½ months, and death resulted from occlusion of both coronary arteries. Unfortunately, even in retrospect, no clinical information pointed to the correct diagnosis in this patient. An aortogram at the time of cardiac catheterization could have shown the thrombus in the sinus of Valsalva.

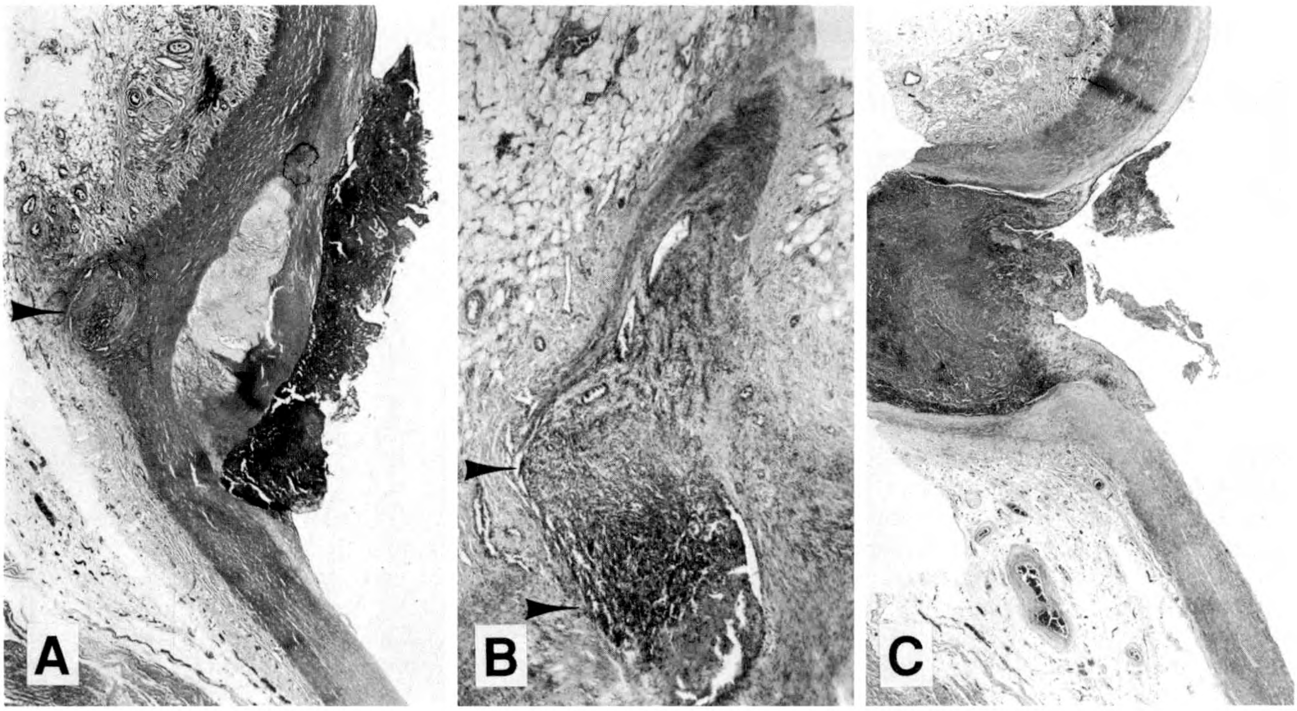

Fig 2. Sections taken at the levels shown in Figure 1A. (A) On the left margin of the right coronary artery ostium, luminal thrombus overlies a small atherosclerotic plaque. This thrombus resembles that occluding the left main coronary artery. The avulsed branch of the right coronary artery, filled by older organized thrombus, is at the arrowhead. *(B) The avulsed artery close to its origin from the right coronary artery. The disruption of its wall may be seen between the two* arrowheads *and the organized thrombus arises from the site. (C) Section through the longitudinal axis of the right coronary artery showing organizing thrombus occluding its lumen. (All hematoxylin and eosin; A and C ×10, B ×35 before 18% reduction.)*

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Tricuspid Valve Incompetence Caused by Nonpenetrating Thoracic Trauma

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Tricuspid valve incompetence from ruptured papillary muscle or chordae as a result of nonpenetrating trauma is uncommon. Blunt trauma causing partial detachment of a leaflet from the annulus is very rare. We report the case of a young adult involved in a car accident who had these findings. Operative repair with resuture of the leaflet to the annulus and annuloplasty using a Carpentier ring resulted in complete recovery.

(Ann Thorac Surg 1991;51:320–2)

A 43-year-old man was in good health until he suffered a blunt trauma in an automobile accident in June 1985. He was thrown against the steering column resulting in fractures of ribs 4, 5, and 6 on the left side. The electrocardiogram showed nonspecific ST- and T-wave abnormalities in the precordial leads. The patient had no previous symptoms nor signs of heart disease. His convalescence was rapid, and he returned to work. However, 2 months later, the patient noted distended neck veins not present before the accident. He was clinically well for 4 years until he began having dyspnea in 1989. He was treated with digitalis and diuretics and was then transferred to the Department of Cardiothoracic Surgery of Casa di Cura Villa Maria for further evaluation.

On examination, he was obviously short of breath and appeared chronically ill. His blood pressure was 120/90 mm Hg; pulse rate was 90 beats/min and regular. The respiratory rate was 20 breaths/min, and his temperature was normal. Large V waves suggesting tricuspid insufficiency were present in the neck veins. A grade 4/5 holosystolic murmur was heard loudest medial to the left ventricular apex. The liver was enlarged. Hematological data were within normal limits. The chest roentgenogram showed cardiac enlargement. The electrocardiogram showed sinus tachycardia with nonspecific ST- and T-wave abnormalities. The echocardiogram showed paradoxical septal motion and dilatation of the right ventricle. Cardiac catheterization demonstrated marked tricuspid regurgitation with enlarged right ventricle, whereas the left cardiac chambers and coronary arteries were normal.

On June 1989, a median sternotomy was performed. Pericardial adhesions were present. The right atrium and ventricle appeared dilated and abnormally thin. On cardiopulmonary bypass, the right atrium was opened. The anterior tricuspid valve leaflet was partially detached from the annulus along three quarters of its length. The chordae tendinae were normal, but the annulus was dilated (Fig 1). The detached leaflet was stitched back to the annulus with a double row of running 5-0 Prolene suture, and annuloplasty was performed using a No. 34 Carpentier-Edwards ring (Fig 2). Cardiopulmonary bypass was terminated uneventfully, and the patient's postoperative course was smooth. The echocardiogram showed a competent tricuspid valve. Four months later, the patient was asymptomatic and was working full time with no exercise restrictions.

Comment

Traumatic tricuspid valve incompetence can result from rupture of papillary muscles, chordae disruption or detachment, rupture of the valve leaflets, or complete valve destruction [1–4]. The physical forces producing this type of lesions may result in seven mechanisms: direct, indirect, compressive, decelerative, blast, concussive, and combined. Indirect force produces an increase in intravascular hydrostatic pressure by sudden compression of the abdomen and extremities. Any violent compression of the heart during diastole associated with some obstruction to great vessel outflow can cause rupture of the chordae tendineae or papillary muscle with resultant insufficiency [1, 4]. The most frequently quoted clinical example of cardiac rupture caused by indirect force concerns the ruptures of chordae tendineae and papillary muscle, whereas the most infrequent lesion results in the isolated tricuspid valve laceration [5].

Symptoms have generally been mild and usually consist of fatigue, dyspnea on exertion, and occasional orthopnea. Their onset may be immediate or delayed and is related to the degree of regurgitation present. In the ruptured papillary muscle group, symptoms usually begin soon after trauma. The most distinctive manifestations are the physical evidence of large V wave venous pulsations in the neck and an enlarged pulsating liver [6]. The hepatojugular reflex is positive. A grade 1/2 systolic murmur may be heard at the left lower sternal border, and it will frequently increase on inspiration. Cardiac enlarge-

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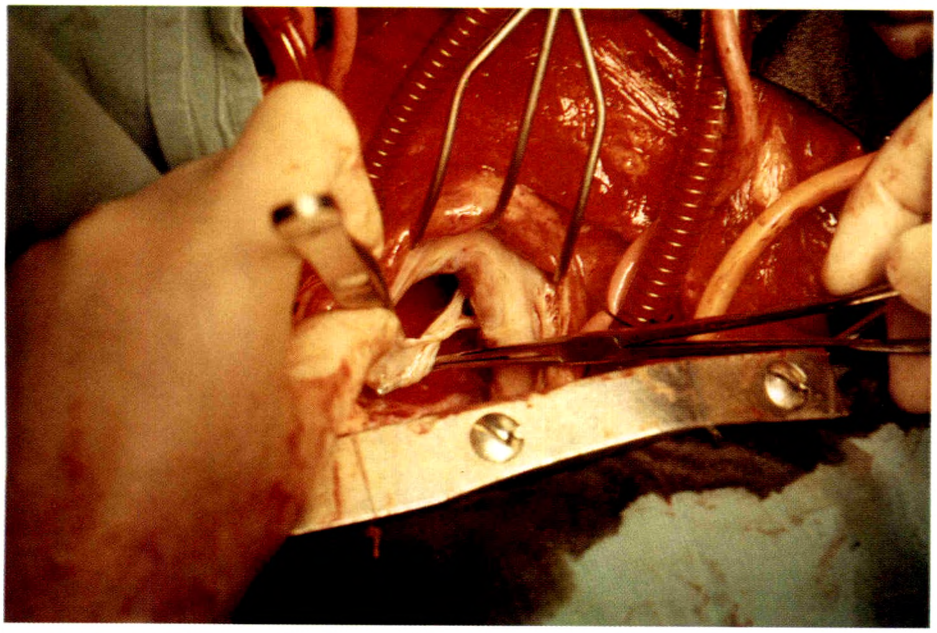

Fig 1. Intraoperative view. Note the line of detachment of the anterior leaflet of tricuspid valve from its native annulus.

ment usually occurs gradually. The electrocardiogram shows an incomplete or complete right bundle-branch block pattern with frequently a P wave of right atrial enlargement [7]. Cardiac catheterization shows reflux of contrast medium into the right atrium and the cavae. Right atrial pressure is high, and the cardiac output may be low.

The timing of operation depends on the clinical situation. Current experience seems to suggest that all patients will eventually require operation. An operation should be recommended promptly in the presence of chronic right-sided cardiac failure not relieved by medical management. It has been reported that some cases of traumatic tricuspid insufficiency due to ruptured chordae may have a relatively benign course, with long-term survival without operation [6, 8].

Papillary muscle and valve reconstruction is the preferred method of management [5], but good results may also be obtained with valve replacement [9].

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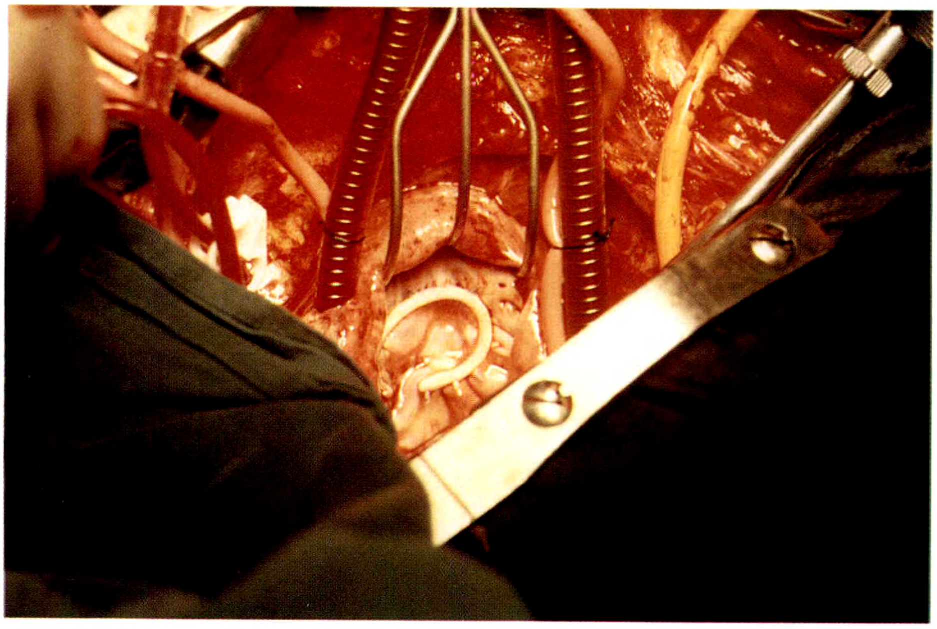

Fig 2. Intraoperative view. The leaflet of the tricuspid valve is stitched to its annulus, and annuloplasty is performed using a Carpentier-Edwards ring. Note the good continence of the valve after repair.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1993 may begin the recertification process in 1991. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1991. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Exchanging Double-Lumen for Single-Lumen Endotracheal Tubes After Thoracotomy

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Three practical methods are described that allow the exchange of a double-lumen for a single-lumen endotracheal tube in patients in whom continued ventilatory support is necessary after thoracotomy.

(Ann Thorac Surg 1991;51:323–4)

Double-lumen endotracheal tubes are now used routinely to ventilate patients during thoracotomy because they facilitate exposure and eliminate the trauma caused by compression of the inflated lung. When continued ventilatory support is required at the completion of a thoracotomy, it is common practice to replace the double-lumen tube with a single-lumen endotracheal tube. This avoids the potential obstruction of the airway that can occur when the small-caliber lumens of the double-lumen endotracheal tube become plugged by secretions. Exchanging the endotracheal tubes can be difficult or even hazardous if the thoracic procedure has been lengthy and if facial or airway edema has developed. We describe three methods that allow easy replacement of the double-lumen tube by a single-lumen tube in this situation.

Material and Methods

The key component in all three methods is the Eschmann stylet (Connell Neurosurgical, Exton, PA). This is a semirigid rod 0.5 cm in diameter, 60 cm in length, and made of woven linen fibers embedded in a resin. The Eschmann stylet is rigid enough to act as an obturator but flexible enough that it does not readily cause mechanical injury to the airway. It is easy to use the Eschmann stylet as an obturator for a single-lumen endotracheal tube because the stylet is much longer than the tube. Unfortunately, the Eschmann stylet is not much longer than a double-lumen endotracheal tube, and it is impossible to withdraw the tube over it without losing control of the position of the stylet. Each of our methods provides a solution to this problem.

The first method is illustrated in Figure 1. The double-lumen tube is amputated just distal to the junction of the two lumens. This leaves 2 to 3 cm of tube protruding from the patient's mouth and makes the tube short enough to withdraw it without losing control of the stylet. A straight hemostat is applied to the side of the endobronchial lumen as a handle to hold the tube in position. The Eschmann stylet is copiously lubricated with viscous Xylocaine (lidocaine hydrochloride) and is passed down the full length of the tracheal lumen. This length can be calculated ahead of time by comparison with an unused endotracheal tube and marked on the stylet with an indelible felt pen. The double-lumen tube is removed over the stylet. A single-lumen endotracheal tube, the interior of which has also been lubricated with viscous Xylocaine, is passed over the stylet and the patient is reintubated. Retraction of the tongue with a laryngoscope facilitates the otherwise blind passage of the endotracheal tube. The stylet is withdrawn after the tube has been positioned appropriately in the trachea.

The second method is illustrated in Figure 2. It is similar to the first method but does not require amputation of the double-lumen tube. Instead, a rigid bronchoscopy forceps is used to grasp the proximal end of the stylet. It acts as an additional length of obturator over which the double-lumen tube can be withdrawn while maintaining the

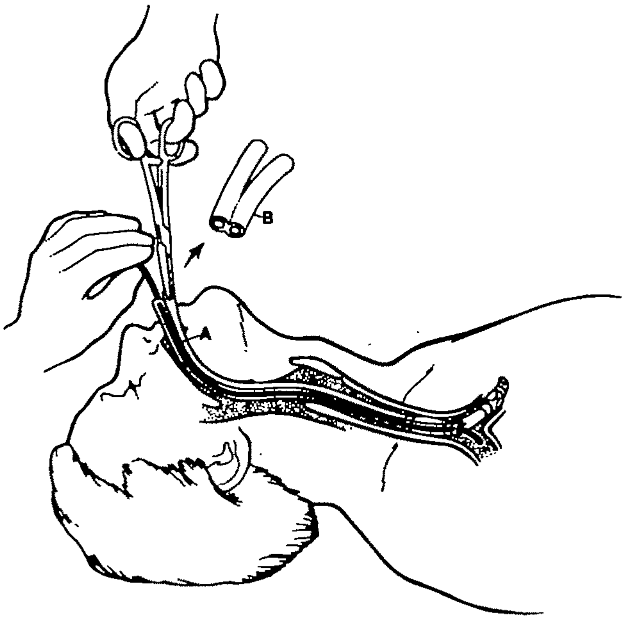

Fig 1. The Eschmann stylet (A) is inserted down the tracheal lumen after the double-lumen endotracheal tube (B) has been amputated just below the junction of the two lumens. A straight hemostat placed on the end of the endobronchial lumen provides countertraction for insertion of the stylet.

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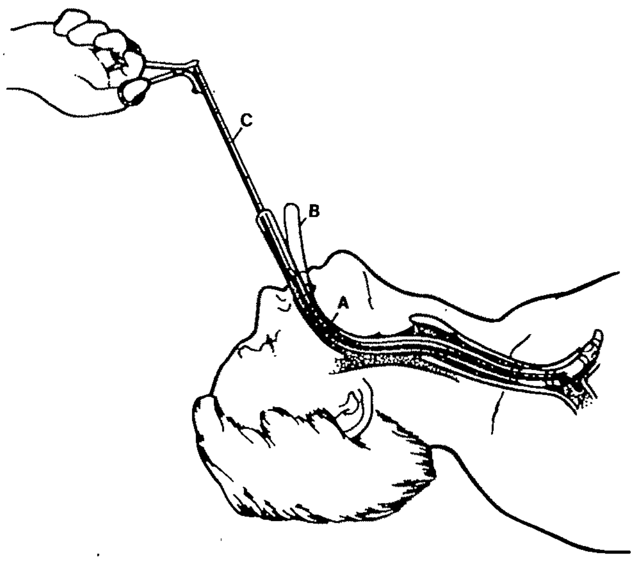

Fig 2. The Eschmann stylet (A) has been passed down the tracheal lumen of the double-lumen tube. Countertraction is provided by manually grasping the end of the endobronchial lumen (B). A rigid bronchoscopy biopsy forceps (C) is used as an extender for the Eschmann stylet.

stylet in position. When the double-lumen tube has been removed, the single-lumen tube is passed over the stylet as described in the first method.

The third method is illustrated in Figure 3. Once again the double-lumen tube is left full length. The Eschmann stylet is placed in the groove created by the junction of the two lumens and is passed alongside rather than through the tube. When the stylet has been inserted through the premeasured length of the tracheal lumen, the tube is removed, and the single-lumen endotracheal tube is passed over the stylet as described in the first method.

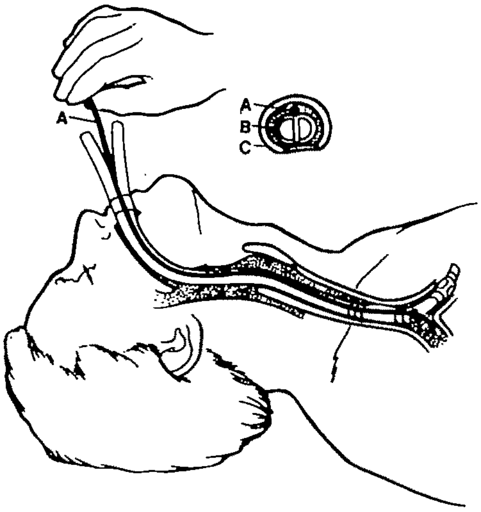

Fig 3. The Eschmann stylet (A) is placed in the groove created by the junction of the two lumens (B) and passed alongside rather than through the double-lumen endotracheal tube (C).

Comment

Double-lumen endotracheal tubes have become a standard part of the intraoperative management of thoracic patients since they were first described by Carlens [1] in the 1950s. They facilitate exposure by allowing selective ventilation and by protecting the dependent lung in patients in whom there is bleeding or infection in the lung on the operated side [2]. Double-lumen endotracheal tubes require continuous monitoring, though, because the small-caliber lumens can easily become obstructed by secretions or blood clot and because accidental overinflation of the bronchial cuff can cause airway rupture. Double-lumen tubes, therefore, are not generally used outside of the operating room. Replacement of double-lumen by single-lumen endotracheal tubes is considered standard practice for patients who need continued ventilatory support at the completion of thoracotomy [3].

Use of the Eschmann stylet as an obturator for reintubation after rigid bronchoscopy has been reported previously [4]. The approach described is similar to our second method. The Eschmann stylet is inserted through the bronchoscope, which is then withdrawn. A rigid bronchoscopy biopsy forceps is used as an extender for the stylet. The single-lumen endotracheal tube is passed over the stylet. Freund and colleagues [5] have also reported using a modified Eschmann stylet as an obturator for the intubation of a patient whose abnormal airway precluded intubation with standard techniques. We have used these methods over the past 4 years and have found each of them to be equally satisfactory.

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Easy Removal of Surgically Placed Intraaortic Balloon Pump Catheter

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This technique simplifies the surgical insertion and removal of an intraaortic balloon catheter using a pledgeted mattress suture and a vascular tourniquet.

(Ann Thorac Surg 1991;51:325–6)

In the occasional patient in whom percutaneous placement of an intraaortic balloon pump catheter is not technically feasible, as in patients with small-caliber vessels or on cardiopulmonary bypass [1], direct surgical insertion is required. The technique we describe simplifies surgical insertion and allows quick and easy removal in the intensive care unit.

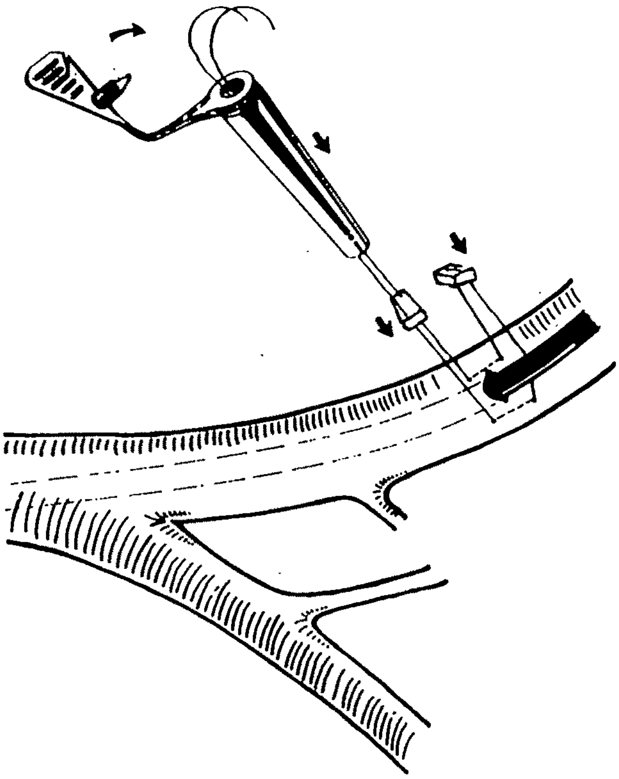

Fig 1. Double Teflon-pledgeted horizontal mattress suture with a vascular tourniquet surrounding entrance site of an intraaortic balloon pump in the common femoral artery.

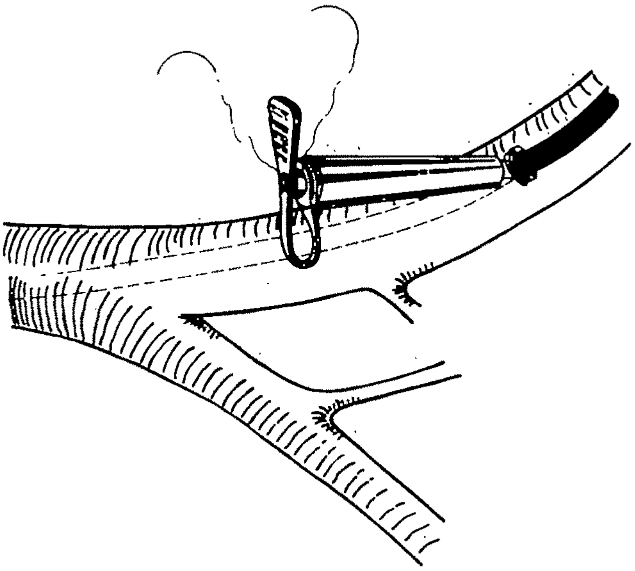

Fig 2. Vascular tourniquet cinched up to be left beneath the skin and subcutaneous tissues for later removal in the intensive care unit.

The catheter is inserted in the operating room through a transverse arteriotomy. A double Teflon-pledgeted 3-0 Prolene (Ethicon, Somerville, NJ) horizontal mattress suture is then placed in the artery with the free ends

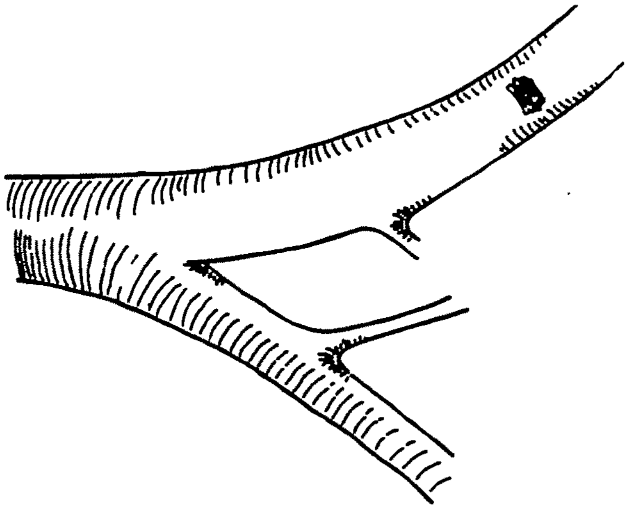

Fig 3. Intraaortic balloon pump and vascular tourniquet have been removed in the intensive care unit and the suture has been secured.

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pointing cephalad (Fig 1) and then secured using a Rumel vascular tourniquet (Fig 2). The tourniquet is left buried beneath the skin and subcutaneous tissues as they are closed.

Removal of the catheter is performed in the intensive care unit with the patient under local anesthesia by first opening the wound and obtaining digital control below the insertion site. The tourniquet is then loosened and digital control is obtained above the insertion site after the catheter is pulled. The artery is sequentially flushed, the tourniquet is removed, and the pledgeted suture is tied (Fig 3). The wound is then closed in routine fashion.

In 15 patients we have had no pseudoaneurysms, strictures, or embolic complications and all wounds have healed primarily without signs of infection. The median time for removal is only 13 minutes. Our initial technique using a pursestring suture was abandoned because of a postoperative stricture.

In conclusion, this technique for placement and removal of a surgically placed intraaortic balloon catheter is not only quicker and easier than traditional methods but also has fewer complications.

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Improved Technique for Inserting a T Tube in Patients With Subglottic Stenosis

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An improved method for inserting a silicone T tube through a tracheostomy stoma in patients with subglottic stenosis is presented. A silicone T tube is pulled into the trachea with a catheter that is inserted into the tracheostomy stoma, advanced through the stenotic subglottic space, and pulled out the mouth. A cone-shaped dilator is placed beforehand at the proximal end of the vertical limb of the T tube to facilitate the passage of that end through the stenotic subglottic space. This method was used in 4 patients with good results. We suggest this technique be tried when attempts to insert a T tube by the usual method fail, as it can be performed under local anesthesia without special instruments and is technically easy.

(Ann Thorac Surg 1991;51:327–9)

A silicone rubber T tube is widely used for the management of various airway problems. It is usually inserted through a tracheostomy stoma by forcing in the vertical portion of the tube with Kelly forceps as described by Montgomery [1, 2]. Because a silicone T tube kinks or folds when forced into a small lumen, it is difficult to insert through a tracheostomy stoma by the usual technique in patients with subglottic stenosis. Here we present an improved technique for inserting a T tube through a tracheostomy stoma in such patients.

Material and Methods

Four patients with subglottic stenosis had insertion of a silicone T tube through a tracheostomy stoma using our technique. The cause of the subglottic stenosis was tuberculosis in 2 patients, a previous tracheostomy in 1 patient, and relapsing polychondritis in 1 patient. All patients had previously undergone a tracheostomy, and a tracheostomy tube had been inserted. In 3 patients, the procedure was performed under local anesthesia, and in 1 patient, who required laser vaporization of the stenotic subglottic space, it was carried out under neuroleptic analgesia. Insertion of a T tube by the usual technique was attempted in each patient but without success. The cause of failure was kinking or folding of the proximal vertical limb of the T tube because of various degrees of subglottic stenosis. The decision was made to try the new technique.

The technique is depicted in Figures 1 and 2. The patient is placed in the supine position on the operating table, and intramuscular sedatives are given. The trachea, larynx, and oropharynx are anesthetized with 4% lidocaine hydrochloride spray. Before the procedure, a cone-shaped dilator (dilator cone) is made from an 8F or 10F Rob-Nel catheter (Argyle). (A dilator cone made from a Rob-Nel catheter matches a T tube up to 11 mm in external diameter.) The external diameter of the wider end of the catheter is cut to match the external diameter of the T tube, and the narrower end is cut so as to allow another catheter to be pulled through its lumen. Another Rob-Nel catheter is inserted through the horizontal limb of the T tube and is pulled out the proximal end of the vertical limb; the dilator cone is placed on the proximal end (see Fig 1).

The Rob-Nel catheter carrying the T tube and dilator cone is inserted into the tracheostomy stoma, advanced proximally into the oropharynx, and pulled out the mouth (Fig 2A). The patient is told to hold his or her breath for a short time. The narrow end of the Rob-Nel catheter is pulled vigorously, and the proximal end of the T tube is passed through the stenotic subglottic space with the aid of the dilator cone (Fig 2B). When the distal portion of the vertical limb is long, it is inserted before the proximal portion. In this case, Kelly forceps are used to facilitate the insertion of the distal portion of the vertical limb (Fig 2C). When the T tube is in the appropriate position, the Rob-Nel catheter is pulled back slightly through the vertical limb of the T tube. The wider end of the catheter is cut off, leaving the tapering portion. The catheter is pulled out the mouth, and the dilator cone is retrieved (Fig 2D).

Results

With this technique, the T tube was successfully inserted in each patient.

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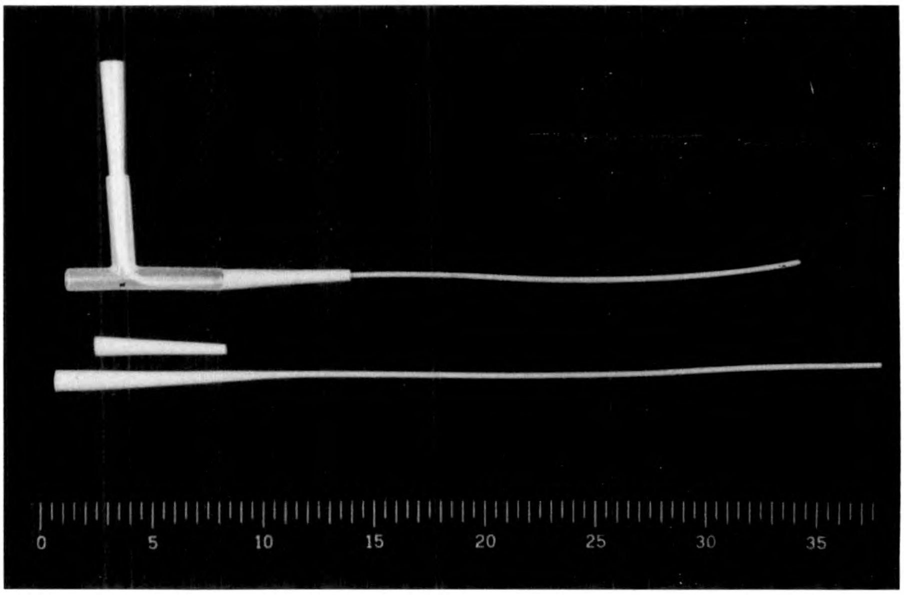

Fig 1. An 8F Rob-Nel catheter (Argyle) and a dilator cone made from the same kind of catheter (bottom). The Rob-Nel catheter is inserted through the T *tube and the dilator cone before the procedure (top). (Scale in centimeters.)*

Comment

A silicone T tube can be inserted into the trachea through a tracheostomy stoma because it is flexible. Because of this flexibility, however, some difficulties can be encountered in placing the T tube in the stenotic airway when the internal diameter of the airway is smaller than the external diameter of the T tube or when there is little clearance

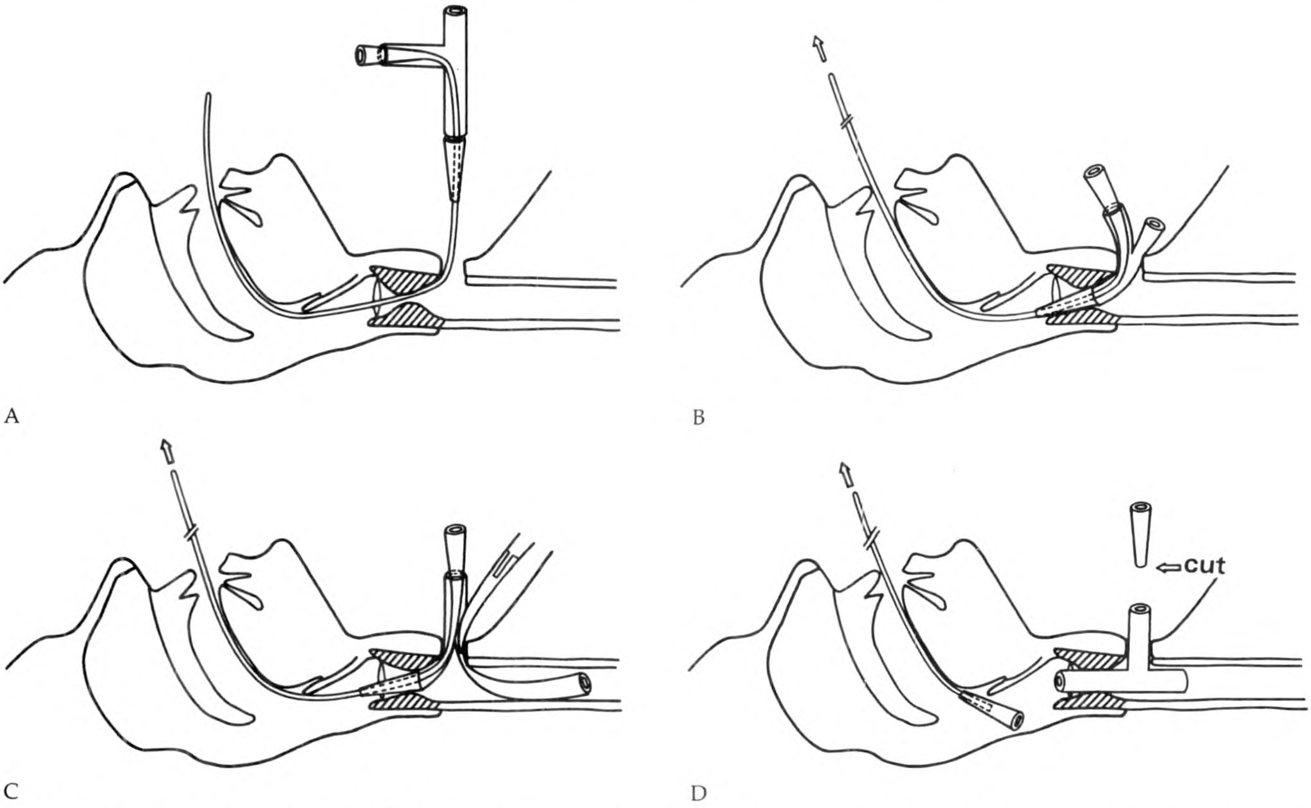

Fig 2. (A) The Rob-Nel catheter carrying the T *tube and dilator cone is inserted into the tracheostomy stoma and pulled out the mouth. (The vertical limb of the* T *tube is depicted horizontally and the horizontal limb vertically because of the supine position of the patient.) (B) The tip of the Rob-Nel catheter is pulled vigorously. The cone-shaped dilator facilitates the insertion of the proximal portion of the vertical limb through the stenotic segment. (C) When the distal portion of the vertical limb is long, it is inserted first. The proximal portion is folded onto the distal portion and inserted with the help of the Rob-Nel catheter. Forceps are used to facilitate insertion of the distal portion. (D) When the* T *tube is in the proper position, the Rob-Nel catheter is pulled back a little through the vertical limb of the* T *tube. The catheter is cut at the tapering portion, and the dilator cone is retrieved by pulling the catheter out the mouth.*

between the lumen and the T tube. This is especially true when the cause of the stenosis is cicatricial rather than tumor related because the elasticity of the airway is more limited with the former.

When the stenosis is distal to the tracheostomy stoma, a tube made of a material harder than silicone rubber (usually a tracheostomy tube) is inserted to dilate and stent as a primary treatment. After an appropriate lumen has been obtained, the tube is changed to a silicone T tube. If the stenosis exists proximal to the tracheostomy stoma, the stenosis cannot be dilated and stented in this way. In this case, some authors describe using a rigid bronchoscope as a dilator before inserting a T tube. Duvall and Bauer [3] reported a technique for inserting a T tube through a stenotic subglottic space by carrying the T tube on a rigid bronchoscope and pulling out the horizontal limb with suture material, which beforehand is tied to it and taken out through the tracheostomy stoma.

Cooper and colleagues [4] modified the usual technique of insertion by facilitating the placement of the proximal portion of the vertical limb with umbilical tape, which is passed through the horizontal limb and proximal portion of the vertical limb and is pulled out the mouth through a rigid bronchoscope. Shapsay and co-workers [5] showed that a folded proximal portion of the vertical limb in the trachea could be straightened by pulling the proximal end of the vertical limb with a forceps through a rigid bronchoscope. With our new technique, a T tube can be inserted without prior dilation of the airway and without the aid of a rigid bronchoscope because it can be pulled into the trachea with the help of the dilator cone.

Our improved technique for inserting a silicone T tube in patients with subglottic stenosis has several advantages: (1) No bronchoscope is necessary for the insertion. (2) The technique can be performed under local anesthesia. (3) The technique need not be performed in an operating room. (4) Fewer personnel are required. (5) The procedure is technically easy. We think that when the T tube cannot be placed by the usual method, our technique should be tried before other more complicated techniques of insertion are used.

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Apical Aortic Cannulation: Application of an Old Method With New Paraphernalia

Francis Robicsek, MD

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An instrument assembly consisting of a special aortic cross-clamp and double-lumen perfusion cannula is presented. The application of these instruments allows occlusion of the ascending aorta traversed by the perfusion cannula inserted directly or through the apex of the heart as well as simultaneous left ventricular venting.

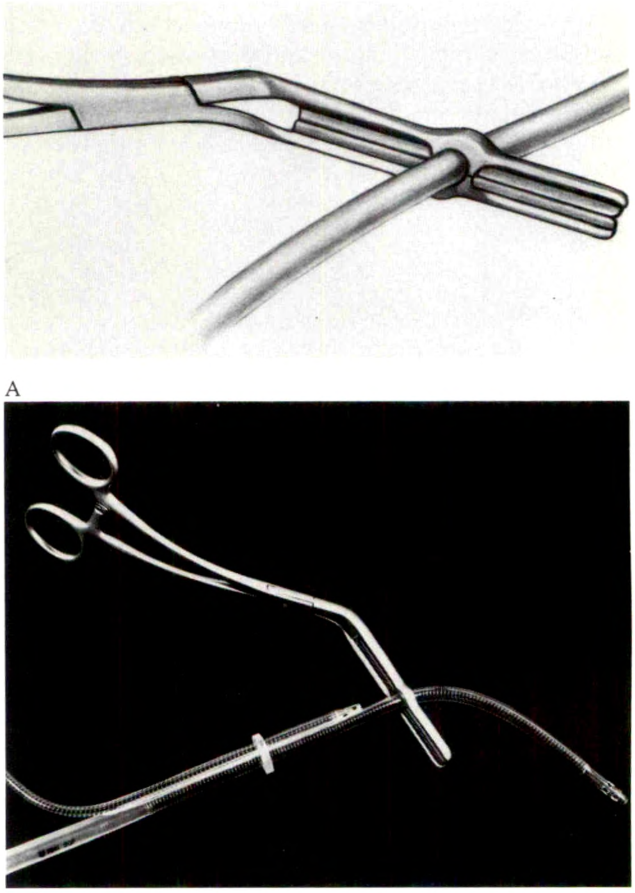
(Ann Thorac Surg 1991;51:330–2)

The ascending aorta is the preferred arterial cannulation site for most if not all cardiac surgeons. If for some reason this site seems to be undesirable, such as in the case of aortic arch dissection, most surgeons choose the femoral artery instead. There are, however, situations where aortic arch pathology extends to, or is associated with, peripheral arterial disease and either of the above two approaches may seem to be inadvisable. In such situations my colleagues and I have recommended aortic cannulation via either the apex of the left ventricle and aortic valve, as first applied by Ormond Julian (Najafi, 1989, personal communication), or directly through the divided ascending aorta [1, 2]. The difficulty that may arise in the application of such "forward" perfusion is that, when and if in the course of the operation cross-clamping of the ascending aorta becomes desirable, it is prevented by the arterial perfusion cannula, which traverses the planned cross-clamping site (Najafi, 1989, personal communication). In the past we tried to overcome this problem by applying a modified Cooley vena cava clamp [2]. Because of difficulties in positioning and the incomplete closure of the jaws of this all-metal instrument around the arterial cannula and diseased aorta, this approach proved to be less than ideal. The purpose of this report is to describe the mechanical features as well as possible applications of a different clamp and perfusion catheter assembly that allows extended indications for forward aortic cannulation.

Technique

The device here described is a padded vascular clamp (Heinrich Ulrich Company, Ulm, Germany) of the Fogarty vascular clamp [3] family. The special feature of the instrument is its length (7.5 cm) and the fact that in its midriff it allows the passage of a perfusion cannula (Fig 1A). This way, whenever the ascending aorta that is traversed by the perfusion cannula is clamped, the device will be occlusive enough to effectively and in an atraumatic way approximate the aortic wall and at the same time confine the blood flow to the distal lumen; it will prevent seepage around but will not crush and obturate a perfusion cannula of appropriate wall thickness and caliber.

As far as the perfusion cannula is concerned, any F20 or


A

B

Figure 1. Application of the special "double-padded" clamp and perfusion cannula. The jaws of the instrument may be brought into a position to fully occlude the clamped aorta but still allow the passage of and unobstructed flow through the intraaortic cannula. The double-barreled cannula allows perfusion through the larger, longer channel tip, which is placed into the aorta, and venting through the shorter, smaller channel, which terminates within the left ventricle.

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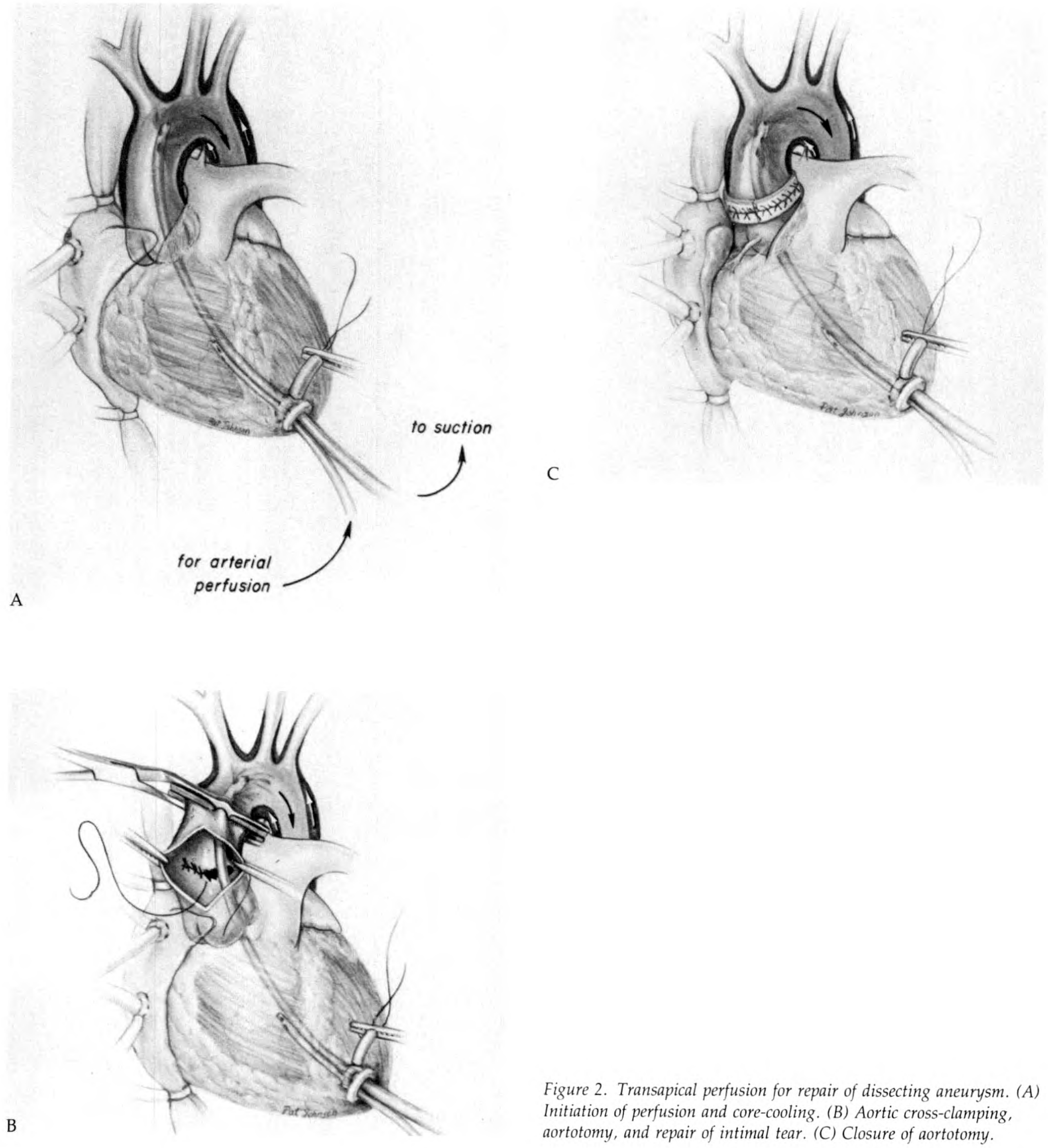

Figure 2. Transapical perfusion for repair of dissecting aneurysm. (A) Initiation of perfusion and core-cooling. (B) Aortic cross-clamping, aortotomy, and repair of intimal tear. (C) Closure of aortotomy.

F22 venous drainage cannula may suffice to be used for apical cannulation; however, we recommend our special double-lumen cannula (Research Medical, Inc, Salt Lake City, UT) (Fig 1B) that allows aortic perfusion with simultaneous left ventricular venting. Transapical perfusion may also be used in a variety of conditions such as mitral valve replacement or reoperation for coronary artery disease when, for various reasons such as calcification at the planned cannulation site or presence of multiple coronary bypass grafts, the surgeon wants to avoid direct aortic cannulation and retrograde femoral perfusion is not feasible. In such situations the left ventricle may be vented through a double-lumen perfusion cannula.

Applications of this method in aortic dissection are shown in Figures 2 and 3.

In 3 clinical cases in which it was applied, two dissections and one coronary reoperation, the instrument proved to be reliable and easy to use.

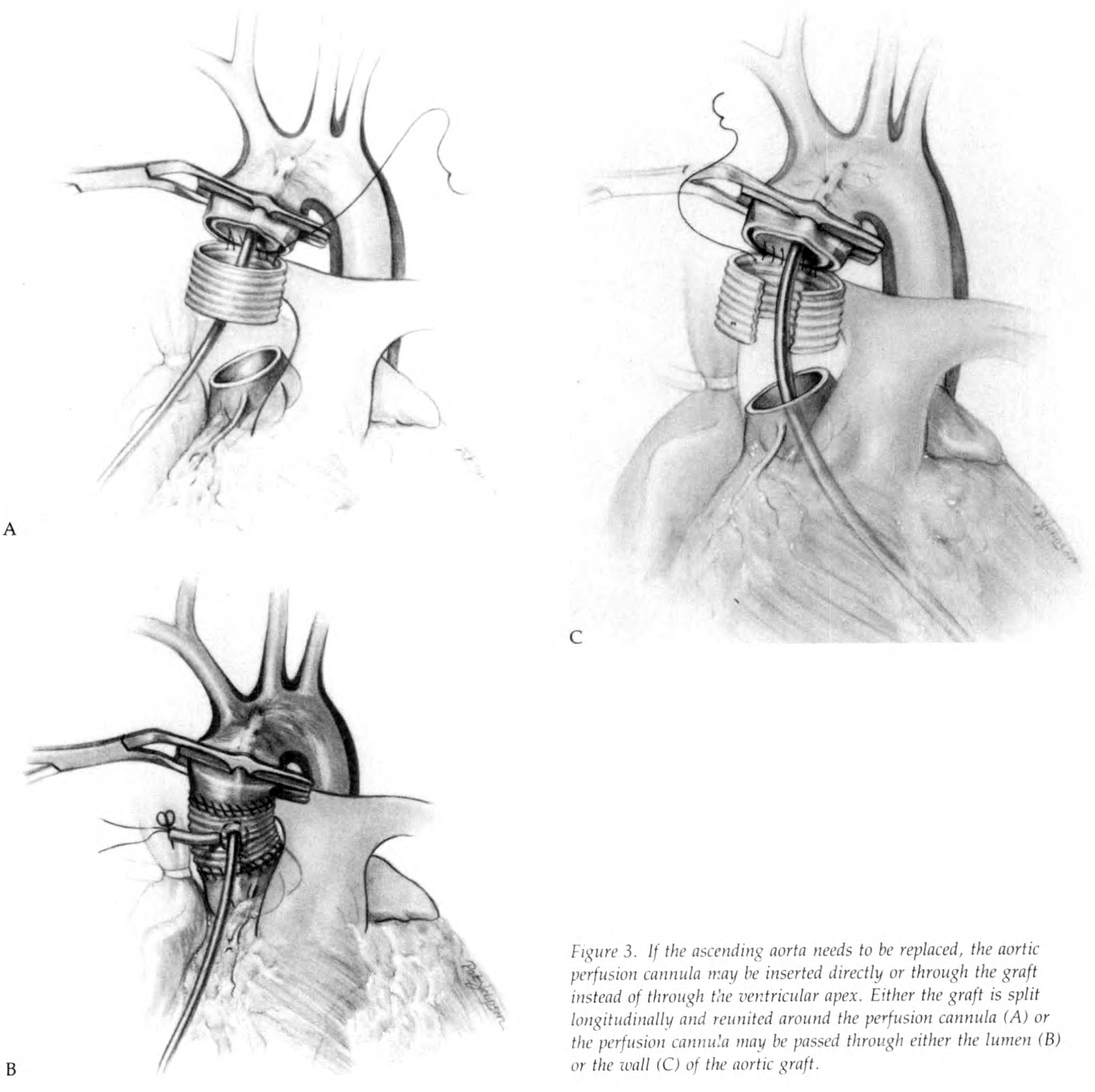

Figure 3. If the ascending aorta needs to be replaced, the aortic perfusion cannula may be inserted directly or through the graft instead of through the ventricular apex. Either the graft is split longitudinally and reunited around the perfusion cannula (A) or the perfusion cannula may be passed through either the lumen (B) or the wall (C) of the aortic graft.

Comment

Aortic perfusion via the left ventricular apex or through the divided ascending aorta itself is an appropriate alternative to direct transaortic or retrograde femoral cannulation in special situations. The indications for this method may be considerably extended by application of the special aortic cross-clamp and perfusion cannula described in this report.

This research made possible by a grant from the Heineman Medical Research Center of Charlotte, NC.

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The Starr Valve Revisited

James R. Pluth, MD

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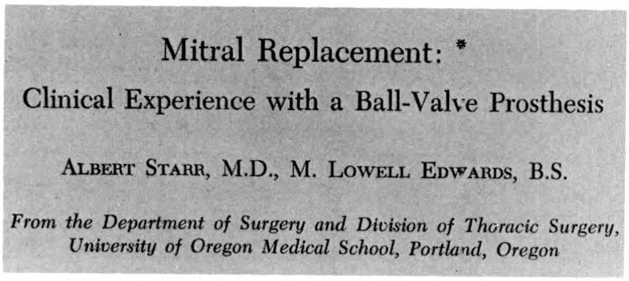
Nearly 30 years have elapsed since Dr Starr's publication introducing the Starr-Edwards valve. Despite reputed difficulties with a ball-and-cage prosthesis, Starr's dedication in developing this concept has resulted in a valve that today continues to be a benchmark of longevity and function.

(Ann Thorac Surg 1991;51:333–4)



Mitral Replacement: *
Clinical Experience with a Ball-Valve Prosthesis

Albert Starr, M.D., M. Lowell Edwards, B.S.

From the Department of Surgery and Division of Thoracic Surgery, University of Oregon Medical School, Portland, Oregon

In October 1961, an article appeared in the *Annals of Surgery* that was destined to radically alter the surgical therapy of valvar heart disease [1]. Surprisingly, it was not a report of the first case of valve replacement nor was it the description of a new valve model. It was simply a report of a long-term survival of 6 of 8 patients in whom a prosthetic valve had been inserted in the mitral valve. It also proved to be the near-attainment of the characteristics that constituted a perfect prosthetic valve.

To provide proper perspective to the enormity of this paper, one needs to be transported to that era. The flavor of the status of the art of valve surgery is perhaps best capsulized by the Proceedings of the Conference on Prosthetic Valves for Cardiac Surgery that was held in Chicago in September of 1960 [2] just 6 months before the presentation of Dr Starr's paper. The status of valve replacement was generally disappointing. Numerous prosthetic designs were presented including the flap valves, disc valves, and ingenious fabrications that simulated the natural valve. Five investigators tallied their experience with the ball-and-cage valve. Schwab concluded that the principle form of complication limiting the successful implantation of the ball valve in the mitral position was thrombus formation in the left atrium. Stuckey reported that the ball caused injury to the wall of the left ventricle, and even Hufnagel, who had been the clinical champion of the ball-and-cage valve, abandoned the concept in favor of a trileaflet design. Starr discussed his experience, and although there had been some success in laboratory animals, the only patient died on the day of operation of an embolic episode. In the end, the Chairman (Merendino) capsulized the results and noted that the efforts with aortic valve replacement were more encouraging, but that mitral valve replacement appeared to be associated with massive clot, infection, septicemia, or cardiac failure. The reasons for these apparent differences appeared to be that the mitral prosthesis did not simulate the natural mitral valve, and the participants left that conference with the admonition that "perhaps materials had been indicted without just cause; perhaps we have concerned ourselves with the function of the valve . . . rather than with serious attempts to approach the natural structure of the valve."

A half-year later, Starr reported long-term survival in patients in whom the ball-and-cage valve had been inserted in the mitral position. Not only had this never been accomplished before, but the paper additionally addressed each of the qualities that the conference had set

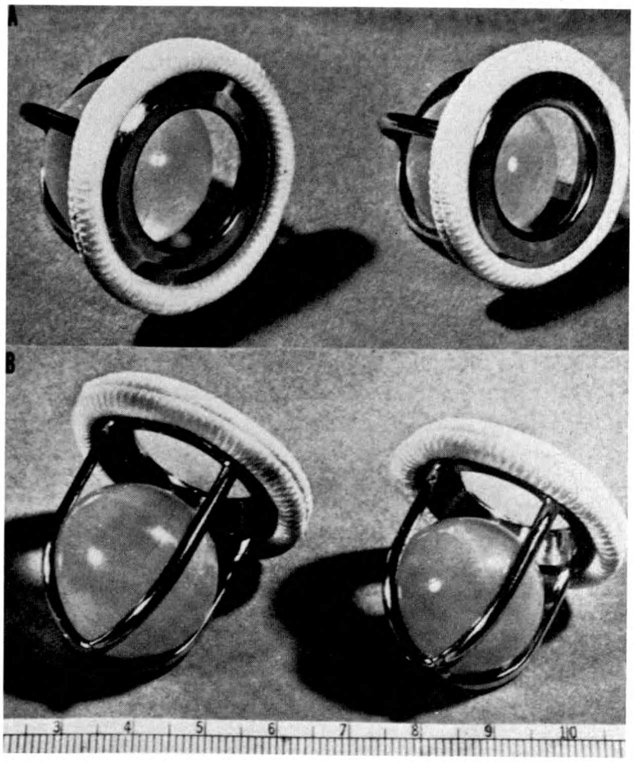


Fig 1. The mitral ball valve prosthesis for human implantation. A. View of inlet side; B. View of outlet side. (Reprinted from Starr A, Edwards ML. Ann Surg 1961;154:726–40, by permission of J. B. Lippincott Co.)

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out to identify the perfect valve. Time has supported the Starr-Edwards valve (Fig 1), and in fact, it remains the gold standard in durability, having been without change since 1965. True, there are today valves that are superior in hemodynamics to the ball-and-cage design, but certainly the Starr-Edwards valve is more than adequate in the majority of instances. Thromboembolism remains a concern, as it does with any mechanical prosthesis, but either due to improved patient selection or more adequate attention to anticoagulation, the risk of this dreaded complication has been reduced. The other desired characteristics of ease of insertion, stable function, tolerance by the blood and tissues, silent function, simplicity of design, and reasonable cost were met.

When one considers the historical problem with valve development, the presentation by Starr seems nearly too optimal. There were but two discussors of the manuscript, and reading within the lines, one can decipher some healthy skepticism, but no one can deny the enormity of the fact that 6 of 8 patients who had had a prosthetic valve inserted in the mitral position were still alive, and 2 had even returned to work.

By mid-1961, the valve was being employed in four nations and in at least five centers in the United States. Subsequently, the use of the valve expanded rapidly and consistently. Starr's manuscript had a substantial impact on the lives of more than 175,000 patients in whom the valve was subsequently employed, while for cardiac surgery, it proved to be the pivotal point in the treatment of valvar heart disease.

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Editor's Note

We asked Dr Starr for a response to Dr Pluth's interesting article.

Dr Starr's Commentary

I am pleased to have this opportunity to comment on Dr Pluth's paper and interject some personal as well as historical notes. I had just completed my residency in thoracic surgery at Columbia Presbyterian Medical Center and had been in Oregon for only a year before I began to work with Mr Lowell Edwards, a retired engineer, on the valve project in 1958. He was in his 60s and I was in my early 30s, but there was no generation gap between us. He wanted to develop a total artificial heart rather than a heart valve and it was only with the promise that the valve would be the first step down that pathway that he felt comfortable about our collaboration. (Of interest, it was only a few years later that Edwards supplied a valve to Dr Willem Kolff for his first artificial heart.) Edwards had the financial resources from previous successful inventions and was totally immersed in this project so we could move very rapidly in testing different kinds of prostheses for mitral replacement.

Dr Herbert Griswold, Chief of Cardiology, and Dr J. Engelbert Dunphy, Chairman of the Department of Surgery, were very supportive; the former by encouraging our first clinical use of the valve, and the latter by paving the way for our presentation at the next meeting of the American Surgical Association.

Edwards went on to establish Edwards Laboratories, at first a small company, then a part of American Hospital Supply Corporation, and currently a subsidiary of Baxter International. From Edwards Laboratories came Don Shiley, Warren Hancock, and Jim Bentley as highly successful spin-offs of this germinal organization. Edwards became the prototype of an enormous industry that keeps our specialty on the road to progress.

In the early days, there was not only a question of the design of the prosthesis, but also the development of surgical approaches to the cardiac valves and the development of methods of myocardial protection and adequate postoperative care. Our use of intermittent cold blood coronary perfusion in the early 1960s allowed us to decrease the mortality of mitral valve replacement from 50% in 1960 to less than 10% in 1965, and to perform multiple valve replacements.

The mitral prosthesis went through a series of rapid changes from 1960 to 1965 and despite all our subsequent efforts, including the development of cloth-covered valves, the performance of the model 6120 mitral could not be surpassed. This was also the case for the aortic prosthesis, the last modification of which in 1968 as a model 1260 remains our usual choice as a mechanical valve for aortic valve replacement.

Dr Pluth has made many kind remarks in this paper concerning the Silastic ball valves. I can only thank him and his earlier colleagues at the Mayo Clinic, including Dr John Kirklin, Dr Robert Wallace, Dr F. Henry Ellis, and Dr Dwight McGoon, who did so much to reduce valve replacement to a standard and predictable operation. As other devices became available in the 1970s they were cautious and deliberate in their selection of valve type, carefully monitoring and reporting their latest results.

Simply put, valve replacement has been in the main a happy story for cardiac surgery with the heart surgeons leading the way in the development of implantable life support systems and setting standards of proper analysis and reporting to be emulated by other specialties.

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Bronchoalveolar Lavage in Lung Transplantation

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One of the dilemmas in the management of lung allotransplant recipients is our inability to precisely determine the cause of graft dysfunction. Differentiating between lung allograft infection, rejection, atelectasis, or ischemic injury remains a difficult task. Tests directed at identifying systemic abnormalities such as peripheral blood analysis so far have been nonspecific and unlikely to accurately and promptly represent changes occurring within the lungs. Transbronchial biopsy and bronchoalveolar lavage have emerged as two methods with the most potential for aiding in the establishment of diagnosis. This review attempts to provide the readers with a current knowledge of the cellular events in lung allograft and the status of bronchoalveolar lavage in experimental and clinical lung transplantation.

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The transplantation of lungs and heart-lungs has now become an accepted therapeutic modality for end-stage cardiopulmonary disease [1, 2]. The actuarial survival rate after 2 years is reported to be around 60% [3]. Graft rejection, infection, and the development of bronchiolitis obliterans continue to be the leading causes of both early and late morbidity and mortality as well as progressive attrition of the lung allografts [4–6].

A definite method for the diagnosis of pulmonary rejection short of open lung biopsy is lacking [7, 8]. In contrast to an earlier report [9], it is now well recognized that pulmonary rejection can occur in the absence of cardiac rejection; hence, endomyocardial biopsy is not a reliable method of detecting lung rejection [10, 11]. Moreover, attempts to differentiate between pulmonary graft infection and rejection have not yet been quite successful. Conventional noninvasive methods such as chest roentgenographs, radionuclide perfusion scans, and pulmonary function tests used in conjunction with clinical assessment have been shown to be nonspecific [12, 13]. The clinical and radiologic improvement on high-dose steroid pulse is used to substantiate the cause as being rejection, but a viral pneumonia will also improve with this treatment. Roentgenographically, rejection as well as infection can similarly manifest as a parenchymal infiltrate or a perihilar flare [13]. Preferential flow to the lung allograft shown on perfusion scan will progressively reverse to reperfuse the native lung in advanced rejection.

Perhaps open lung biopsy remains the gold standard to confirm the diagnosis of rejection and to differentiate it from infectious pneumonia. However, this seems to be quite invasive and hence a decision to perform this may be difficult. Other less invasive methods currently under evaluation are transbronchial biopsy [14–16] and bronchoalveolar lavage (BAL). Bronchoalveolar lavage has recently gained popularity among respirologists for the investigation of mechanisms of lung injury. It has been advocated for the differentiation between various interstitial lung diseases. Except for the identification of bacterial, viral, or protozoal lung infection, the determination of the intensity of alveolitis, and perhaps monitoring its response to medical treatment, so far it has shown little justification for its wide application [17, 18].

When rejection is not detected on histopathologic examination of the lungs, organisms detected in BAL are likely to be involved in the process of lung injury and frequently will warrant treatment. Transbronchial biopsy, advocated by the Papworth group, is likely to be the most specific way of defining lung rejection. Unfortunately, two major limitations for its absolute success exist. First, its sensitivity appears to be dependent on the number of specimens taken. Any time fewer than nine specimens are taken, its sensitivity decreases significantly. Scott and associates [19] recommend that any number between 12 to 15 biopsy specimens be taken. Second, immunocompromised patients with *Pneumocystis carinii*, cytomegalovirus, and *Herpes pneumoniae* show perivascular cuffings in their lungs in a manner similar to that seen in rejected lung allografts [20].

Achterrath and co-workers back in 1975 [21] advocated the use of BAL to differentiate between reimplantation injury and lung rejection. Their canine experiments showed a limited value of BAL perhaps due to the limitations of conventional staining techniques available at that time. Since then, and with the advent of modern-day technology, functional and phenotypic analysis of BAL cells has allowed insight into cellular events in the lung allograft. Furthermore, we now can use BAL to retrieve bacteria, virus, and protozoa that may be etiologic of the lung injury.

This article will not describe the various methods available for the evaluation of the lung allograft. Rather, it will review the current knowledge on the role of BAL in the investigation of cellular events in the lung allograft and its

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plausible clinical applications to the management of lung transplant recipients.

Morphologic Analysis of Bronchoalveolar Lavage Cells

Bronchoalveolar lavage offers a unique opportunity for the safe and repetitive harvesting of large quantities of graft-infiltrating immunocompetent cells. Retrieved cell suspensions do not require complicated cell separation methods to obtain purified lymphocytes as is necessary with tissue fragments of other organs. Studies on graft-infiltrating cells are essential to advance our understanding of the mechanisms of lung rejection as well as for the development of a reliable method to detect and differentiate rejection from various infections in the lung allograft.

The composition of cells harvested from the normal bronchopulmonary compartment has been well characterized in various species [20–24]. Typically, human bronchoalveolar washings contain about 95% macrophages, 4% to 5% lymphocytes, and 0% to 1% polymorphonuclear leukocytes (PMLs). Normal canine BAL cells consist of 65% to 85% macrophages, 10% to 20% lymphocytes, and 4% to 10% PMLs. Many studies were carried out in the canine model to look at the effect of various lung injuries on BAL cell compositions. Achterrath and associates [21] and Whitelaw and co-workers [22], as well as others [25–27], attempted to define changes in BAL cell types after lung autoimplantation and alloimplantation in dogs. Similar studies were also performed in the rat model by Prop and associates [23] as well as others [28, 29]. Our group studied phenotypic and functional changes of BAL cells in the presence of atelectasis [30], warm ischemic injury [31], gram-negative bacterial pneumonia, and allograft rejection in canine models [32]. The goal was to characterize changes in BAL specific to each of these pulmonary injuries and, hence, to attempt a differential diagnosis.

In the past, conventional staining such as the Grumwald-Giemsa method was used to define BAL cells. Differential counts were frequently inconsistent owing to the variations in morphology and staining characteristics within the same cell line. For example, it is particularly difficult to distinguish a small macrophage from a medium or large lymphocyte. Nonspecific esterase (which better defines mononuclear phagocytes) and peroxidase stains were frequently employed to enhance the difference between these two cell populations. In the absence of immunosuppression, rejecting allografts manifested a trend toward polymorphonuclear leukocytosis in BAL cells 3 to 7 days after transplantation. This was usually accompanied by a proportional decrease in the macrophage and lymphocyte populations [22, 26]. Recent studies, using more convincing staining methods, actually showed a steady rise in the absolute number of lymphocytes together with a persistent, but less drastic polymorphonuclear leukocytosis in BAL cells as rejection advances [23, 25, 29]. Similarly in autografts, a significant increase in BAL polymorphonuclear leukocytes (40% to 60% of BAL cells) was observed 2 to 4 days after reimplantation [22, 28, 31]. This, however, was noted to return to normal values after the first week. It hence appears that there is no distinct BAL cellular profile within the first week after allotransplantation or autotransplantation.

The difference becomes more defined 1 week after operation when cellular changes secondary to reimplantation response resolve. Harvesting a large number of BAL cells consisting mainly of PMLs and lymphocytes a week after transplantation, in the presence of radiologic evidence of a new or persistent perihilar and pulmonary infiltrate, would point more toward rejection than toward reimplantation injury. However, the situation may be more complicated. Atelectasis and pneumonia, which frequently occur early in the posttransplantation period, have clinical and radiologic manifestations similar to that of acute allograft rejection. Experimentally, our group has studied changes in BAL cell profiles in controlled animal models of lung allograft rejection, infection, atelectasis, or reimplantation injury. There certainly appears to be strong evidence that conventional total and differential counts of BAL cells cannot differentiate any of these lung pathologies after lung transplantation. Similar observations were made in clinical lung transplantation [33]. Furthermore, the plausible presence of more than one pathologic entity in the postoperative period (ie, atelectasis and rejection or pneumonia and rejection) leading to overlapping BAL cellular profiles makes morphologic examination of BAL cells alone a less valuable method for differentiating rejection from other types of lung injury. More sophisticated immunologic methods have recently been considered to potentiate the role of BAL in the diagnosis of rejection and infection in the lung allograft. These will be discussed in the following sections.

Flow Cytometric Phenotypic Analysis of Bronchoalveolar Lavage Cells

Allograft rejection is a process of dynamic interaction primarily between various specific subpopulations of T lymphocytes, macrophages, B lymphocytes, and PMLs [34, 35]. Bacterial infection, on the other hand, involves mostly nonspecific inflammatory PMLs and macrophages. Lymphocytes play a less dominant role. Mononuclear cell–mediated immunity is the primary host defense mechanism against viral and protozoal infection [36, 37]. Theoretically speaking, examination of BAL mononuclear cell phenotypes in rejection or infection may reveal differences in its cell subsets that may be specific to each of these pathologic entities and, hence, may enable us to distinguish one from the other. Experimentally, Shennib and colleagues [38] studied the difference in cellular phenotypes of BAL and peripheral blood mononuclear cells in a controlled canine model of allograft rejection and gram-negative bacterial pneumonia. Using murine monoclonal antibodies raised specifically against canine mononuclear cell subpopulations, they found that the percentage of mature T lymphocytes was higher in BAL cells from rejected lungs as compared with infected ones. The percentage of cytotoxic/suppressor cells as well as their precursors was higher in BAL cells and peripheral blood lymphocytes of rejecting animals than in those of pneumonic ones. They noted that the ratio of macrophage/T-cell percentages was lower in BAL cells in rejection compared with infection. Although the latter finding appears interesting, its diagnostic value remains unclear. Furthermore, a nonspecific increase in cytotoxic T cells can be observed in other types of lung injuries as well [31, 32].

Clinically, Zeevi and associates from the University of Pittsburgh performed phenotypic analysis of BAL cells in lung allograft recipients during episodes of rejection and infection. Rejection was diagnosed when radiographic infiltrates consistent with rejection were present, infection being excluded with negative cultures, and there was resolution of infiltrate with augmentation of immunosuppression therapy. Infection was confirmed when a pulmonary pathogen was recovered in the absence of rejection. Histologic confirmation was not always available. They found that during acute lung rejection, there was an increase in numbers of macrophages, CD8+ cells (cytotoxic/suppressor T lymphocytes), and neutrophils; during infection, especially with *P carinii* and cytomegalovirus, both CD4+ (inducer/helper T cells) and CD8+ subsets were markedly increased [39–41]. They also noted that an increased CD4/CD8 ratio and a positive primed lymphocyte test (this will be discussed later) in BAL cells may be risk factors for the development of chronic lung rejection in long-term survivors [42]. They suggested that these variables may be useful in monitoring the effectiveness of immunosuppressive therapy.

More recent work by Holland and co-workers [43] showed that there was a gradual increase in the number of CD8+ lymphocytes recovered from nonrejecting, noninfected lung allografts (by clinical criteria) 6 and 12 months after transplantation. In the absence of undetectable subclinical rejection, the importance of such a delayed host response to the allograft in the form of accumulation of cytotoxic/suppressor lymphocytes into transplanted lungs remains unclear. A similar finding was also reported by Gough and associates [44]. Clelland and co-workers [45] from Cambridge, UK, reported that there were significant differences of BAL percentage and absolute lymphocyte counts between acute lung rejection and normal or infected lung on retrospective analysis of BAL cells and clinical status of the lung allografts.

Although reports on phenotypic analysis of BAL cells with monoclonal antibodies in the investigation of lung allograft infection and rejection are still scanty and preliminary, this technique appears to have tremendous potential in the management of lung transplant recipients. It is less time-consuming than functional assays currently investigated; results can be promptly received within a few hours. So far, experimental studies have suggested that different patterns of recovered BAL cells seem to be associated with different pathological lung conditions. However, the question remains, how accurately can BAL cellular changes predict the underlying pathology within the lung allograft?

Functional Analysis of Bronchoalveolar Lavage Cells

Immunologic functions of bronchoalveolar cells from normal lungs have been extensively characterized [46–48]. Emeson and co-workers [49–51] adapted the lectin-dependent cell-mediated cytotoxicity assay, which measures total T-cell cytotoxicity, to study the cytolytic function in BAL lymphocytes in canine lung allografts. A strong correlation was noted between cytotoxicity of the BAL T cells and the clinicopathological severity of rejection. Alveolar macrophages, on the other hand, were found to abrogate the cytotoxicity observed in BAL-harvested T cells. It hence appears that when rejection occurs, either the number of BAL T cells or their cytotoxicity is increased; the down-regulation of alveolar macrophages may also be removed.

Of additional importance in this study is the observation that changes in BAL cell cytotoxicity were noted at an early phase of lung rejection when only pathologic changes in the form of mononuclear cell infiltration around small vessels were present; such changes are usually clinically concealed and precede the later phase of more advanced rejection and graft damage with alveolar space involvement and detectable roentgenographic manifestation. Interestingly, donor-specific cytotoxic T lymphocytes are detected in the graft 24 to 48 hours after the detection of increased lectin-dependent cell-mediated cytotoxicity during a rejection episode. Therefore, surveillance of both lectin-dependent cell-mediated cytotoxicity and donor-specific cytotoxic lymphocytes in BAL cells may appear essential for early and accurate detection of an impending acute allograft rejection. However, results of the lectin-dependent cell-mediated cytotoxicity assay must be interpreted in conjunction with the overall clinical picture because there have been instances of transient increases in intragraft cytotoxic activity without evidence of rejection [51]. For now, the clinical limitation of these assays is the need to retrieve a large quantity of effector cells and the commitment of time and personnel trained to do such assays. This may, for now, be the limiting factor of its clinical application.

Zeevi and associates subjected BAL cells harvested from the lung allograft recipients to a battery of functional studies. They performed (1) spontaneous proliferation assay, which quantitates the degree of allogenic interaction between donor and recipient immunocompetent cells (also referred to as allogenic bronchoalveolar macrophage and lymphocyte reaction) [52, 53]; (2) primed lymphocyte testing, which quantitates the alloreactivity of graft-infiltrating lymphocytes to cells bearing donor antigens [39]; (3) interleukin-2 response assay, which indicates the presence of activated T lymphocytes in BAL cells [52]; and (4) cell-mediated lympholysis assay, which detects donor-specific cytotoxic T lymphocytes in the BAL cells [54]. They observed that lung allografts were infiltrated with reactive donor-specific lymphocytes that could be detected early in the course of rejection and before roentgenographic changes became apparent. They also noted that bronchoalveolar macrophage and lymphocyte reaction was observed to be high in both rejection and *P carinii* infection. The first reaction may represent an alloreactive response of recipient lymphocytes to donor antigens, whereas the increase of bronchoalveolar macrophage-lymphocyte reaction during or after *P carinii* infection might represent a physiologic response in which autologous macrophages and lymphocytes interact to fight invading organisms. Similarly, primed lymphocyte testing was also noted to be increased in both rejection and pneumocystic infection, which suggests that an increased accumulation of donor-specific alloreactive T cells existed with this type of infection. The importance of this increase in donor-specific T cells is not clear. It is possible that *P carinii* infection facilitated the development of a chronic allograft rejection.

Increases in primed lymphocyte testing and CD4/CD8 ratio in BAL cells were also observed at or immediately after cytomegalovirus, Epstein-Barr virus, *P carinii*, and occasionally after bacterial pneumonia [42]. These infection-induced changes have been observed to precede the development of chronic lung rejection, which might be a sine qua non to obliterative bronchiolitis. If infection contributes subclinically to the occurrence of chronic rejection, then theoretically one may use BAL to reveal the presence of either and, hence, the need for defining further the type of infection or, if negative, the need for augmenting immunosuppression. Primed lymphocyte testing has been reported to have 83% sensitivity and 91% specificity in detecting bronchholiolitis obliterans. Phenotypic analysis and primed lymphocyte testing of BAL lymphocytes have been concurrently employed by the Pittsburgh group to monitor chronic lung rejection and the development of obliterative bronchiolitis in human heart-lung transplant recipients [55]. Lung allografts usually carry a various load of passively transferred bronchus-associated lymphoid cells. They can actively participate in the rejection response for a presumably long period of time [56]. These donor bronchoalveolar lymphocytes and macrophages are rapidly replaced with recipient ones within 4 to 6 weeks after transplantation [57].

Recently, it was revealed that a transplanted lung had a reduced capacity to develop an antibody response to locally deposited antigens. It was suggested that antigens in transplanted lungs failed to translocate to draining lymph nodes, resulting in minimal humoral response in blood or lung [58]. Moreover, alveolar macrophages from transplanted lungs demonstrated significantly less accessory capability for the generation of an immune response to mitogen or antigen in vitro [59]. These observations imply that the host defense systems were likely to be severely impaired in the lung allograft. This, among other factors, might explain the particular predisposition to infection.

Kirby and associates [60, 61] studied the frequency of donor-specific cytotoxic lymphocytes (effector cells and their precursors) in alveolar and peripheral blood mononuclear cells in canine lung allografts using the limiting dilution assay technique. They found that the frequency of donor-specific cytotoxic lymphocytes peaked 9 to 14 days after transplantation in nonimmunosuppressed lung allograft with acute rejection. Interestingly, in adequately immunosuppressed lung transplant recipients, there was still a very high sequestration of donor-specific lymphocytes in the grafts. Those grafts showed evidence of the subacute, alveolar type of rejection on histologic examination. Kirby and associates concluded that cyclosporin A may have modified the pathogenesis of pulmonary rejection, even though it had not prevented the accumulation of donor-specific lymphocytes within the grafts. Such studies emphasize the important potential variation in the expected outcome of any BAL test based on the types of immunosuppressants used and the doses at which they are administered.

Other Tests

Not all studies done on BAL are focused on examinations of its cellular components. Bronchoalveolar lavage fluid has also been analyzed for soluble markers of lung allograft rejection or infection. For instance, high levels of thromboxane B_2 in BAL fluid from the lung grafts were strongly correlated with rejection [62]. Moreover, infection and rejection of the lung allografts resulted in distinctly different levels of protein, lipid, and various components of pulmonary alveolar surfactant in BAL fluid [63]. Because rejection is known to be associated with an increase in pulmonary vascular resistance and with shifting of the blood flow to the native lungs, our laboratory is now exploring the role played by vasoactive substances such as angiotensin-converting enzyme and endothelin in the occurrence of this phenomenon. Bronchoalveolar lavage fluid samples are analyzed to see if a correlation between the levels of these vasoactive substances and various causes of lung allograft failure exists.

Finally, BAL has been a valuable tool for the direct diagnosis of causative agents of lung graft infection. Bacterial, viral, and protozoal opportunistic infection can now be identified with relative ease. Gryzan and associates [40] from the University of Pittsburgh reported a very high incidence of postoperative *P carinii* infection (88%) in heart-lung transplant recipients. They reliably and rapidly made the diagnosis of *P carinii* infection by examining cytocentrifuge preparations of BAL cells stained with silver methenamine for cysted forms. In addition to monitoring the increase in cytomegalovirus titers, BAL fluid can be tested for cytomegalovirus by inoculation into human embryonic lung tissue culture, and cytomegalovirus "immediate early antigens" can be detected by immunofluorescence using monoclonal antibody at intervals after inoculation. This technique allows relatively rapid and accurate detection of cytomegalovirus in BAL fluid [64]. Whether the identification of infectious agents in BAL necessarily indicates the presence of lung infection by these agents remains controversial.

Summary

Lung transplantation has become a well-established therapeutic modality for end-stage lung disease in many centers. It has attracted a great deal of clinical and basic research. An accurate, fast, safe diagnostic method for the differentiation of rejection from infection of the lung allograft remains elusive. Bronchoalveolar lavage, among other techniques currently under investigation, has been extensively employed and refined as a method to study and to attempt diagnosis of lung allograft rejection and infection. Bronchoalveolar lavage samples are routinely sent for bacterial and viral studies. Furthermore, phenotypic and functional analysis are also frequently performed.With refinement of our technique and the accumulation of more concrete data, it is hoped that within the near future we may have in our hands a relatively simple and rapid noninvasive method for the detection of the cause of lung allograft injury as well as for monitoring the adequacy of immunosuppression and the prevention of chronic rejection and bronchiolitis obliterans.

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Human Immunodeficiency Virus and the Thoracic Surgeon

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I attended two conferences at The Centers for Disease Control (CDC) this year. The first was for the purpose of developing a strategic plan for the surveillance, investigation, prevention, and control of occupationally acquired human immunodeficiency virus (HIV) infection in surgical and obstetrical personnel. The second 2-day conference was for the express purpose of developing a plan to prevent bloodborne pathogen transmission from infected health care workers to patients during invasive procedures.

I learned much during these sessions and some information may be of interest to thoracic surgeons. Unless specifically referenced, the following factual information was presented by the CDC officials as the current data at the time of the conference and is not necessarily previously published material.

Risk to Surgeons From Infected Patients

Other than the overall acquired immunodeficiency syndrome (AIDS) case surveillance through the Public Health Service and the CDC, there has been no systematic national surveillance to determine how many health care workers acquire HIV infection as a result of an occupational exposure. Reporting of AIDS and HIV seroconversions begins at the local and state levels and this information is passed on to the CDC. As of October 31, 1990, there had been 154,917 AIDS cases reported from the 50 states [1]. In addition there are more than one million (perhaps far greater) HIV-positive people, many of them not aware of their status. Five percent of the AIDS cases have been in health care workers, but, because health care workers make up about 5% of the working force in the country, they are not overly represented. Six percent of US health care workers with AIDS are currently classified as having an undetermined risk for HIV infection. This is compared with 3% of workers in other fields in whom the source of the infection is obscure. When the source of infection is listed as undetermined, it usually is because of refusal to be interviewed, because the investigation is still in progress, or because of death before the investigation could be completed. No precise conclusions can be drawn from these numbers to indicate that there is a special risk associated with being a health care worker.

As of July 1990, the CDC was aware of 24 HIV seroconversions among health care workers in the United States following a specific occupational exposure. Another 13 claiming occupational transmission were found to be seropositive, but the dates and source of their infection are not precisely known. These 13 are regarded as suspicious for occupationally related transmission of the disease, bringing the total to 37.

Studies involving a total of 3,978 punctures from needles contaminated with HIV-positive blood have resulted in seroconversion in 13 workers (0.33%) [2–4]. This represents the chance of infection resulting from a needle stick to be 1 in 300. Almost certainly, a puncture with a hollow needle containing blood in the lumen carries a higher risk than a prick by a solid needle with a minimum amount of blood. Most of the exposures in these reported studies have occurred not in the operating room, but on hospital wards and in emergency rooms. Nurses are reported to be the most frequently stuck, followed by physicians and medical students. We have no reliable data on the frequency of HIV seroconversion following needle stick or cuts with sharp instruments in the operating room. Needle-stick episodes in this setting are probably vastly underreported, and the HIV status of most patients in the operating room is unknown.

Even fewer data and less knowledge are available for assessing the risk of exposure of HIV-positive blood to skin surfaces. In prospective surveillance studies to date, with more than 2,000 cutaneous exposures to HIV-positive blood, there have been no seroconversions in more than a year of follow-up. At this time, exposure to intact skin has not been detected as a risk. As every surgeon knows, however, skin, particularly around the fingernails, is never 100% intact, and holes in glove fingers can produce prolonged exposure of patients' blood to the surgeon's skin.

Transmission due to mucous membrane contact is rare but has been documented. The danger of transmission from aerosols of blood created by mechanical saws and drills remains a theoretical threat without definite proof. Certainly the risk from these modes of transmission remains low. There is no doubt that a definite risk of HIV transmission from patients' blood to surgical teams is present, but detailed analysis fails to reveal that the risk to surgeons' lives is higher than they have accepted in the past from other transmissible diseases. There is at this time no suggestion that the risk of HIV transmission to surgeons in the operating room setting is higher than to other workers in other parts of the hospital. The fact that 6% of health care workers with AIDS have not disclosed any of the recognized life-style risk factors does not justify the conclusion that the disease was contracted from a patient in the health care setting. This remains speculative.

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The disease is not easily transmitted [5-8]. This is well supported by the fact that, to date, no transmission has been made by an AIDS patient to a family member living in close contact at home, hugging, kissing, and sharing such things as eating utensils and toothbrushes. The definite threat remains, however, that the disease can be transmitted by small amounts of infected blood to another person by means of cuts, punctures, or exposure to other forms of nonintact skin such as abrasions and rashes. A previous report in *The Annals of Thoracic Surgery* [9] prescribes the universal precautions to minimize the risk of transmission of HIV to workers in health care centers. A recent prospective study reported that cutaneous exposure to blood by surgical personnel (blood splashes or holes in gloves) occurred in 6.4% of operations, and percutaneous or parenteral exposure (needle sticks and cuts) occurred in 1.7% of 1,307 consecutive operations [10]. This observation was made at the San Francisco General Hospital, where the personnel are well aware of the risks, and presumably serious attempts were made to minimize the contact with patients' blood.

Prophylactic Strategy—Local Treatment

Various speculations have been made for local treatment to areas accidentally contaminated during operations, such as a stick in the finger by a needle contaminated with HIV-positive blood. These include local infiltration with povidone-iodine, and even cauterization and local excision of the injured area. Robicsek and associates [11] have suggested that prophylactic local measures may have a sound basis. Radioactive-labeled particulate matter of size similar to the HIV was demonstrated to remain confined to the local area for a few minutes after injection into the subcutaneous tissue of experimental animals. Further studies by Robicsek (Robicsek F, personal communication, 1990), using retroviruses other than HIV, are under way to determine whether these local prophylactic measures are effective.

Prophylactic Strategy—Systemic Treatment

There is a possibility, suggested from animal experiments involving other retroviruses, that prophylactic zidovudine (AZT) given immediately after an accidental occupational exposure may favorably alter the course of HIV infection [12, 13]. The manufacturer of AZT initiated a national double-blind, placebo-controlled study to assess the value of AZT after occupational exposure to HIV. This investigation was stopped, however, owing to low enrollment. It was a complex study and, because of the relatively low risk for infection and other obstacles such as the refusal of subjects to be randomized, it will be years, if ever, before we will learn whether prophylactic AZT is actually effective for the purpose of preventing HIV infection. Because the animal studies suggested that delay in administration of the AZT resulted in loss of effectiveness of the treatment, health care centers should plan in advance either to provide this drug following a recommended protocol or to decide that the evidence does not warrant this prophylactic treatment. If the medical staff of an institution waits until an incident occurs before developing such a plan, there will not be enough time for decision-making and drug procurement to treat the first victim of an accident who desires to follow this course of action. Health care workers are trained to report incidents, and this includes possible accidental exposure to HIV. They have a right to expect to receive evaluation, counseling, and some form of postcounseling management. It should be understood that the effectiveness of prophylactic AZT in preventing HIV infection has not been proven. The Public Health Service cannot make a recommendation for or against prophylactic AZT at this time because of limitation of current knowledge.

Risk to Patients From Infected Surgeons

The latest conference at the CDC was called to help formulate recommendations for the prevention of transmission of HIV from an infected health care worker to a patient during invasive procedures. This was stimulated by the first suspected transmission from an HIV-infected health care worker to a patient. The case report was as follows. A dentist had AIDS and continued working. He performed an invasive procedure (extraction of two molar teeth under local anesthesia) upon a patient whose HIV status before the dental work was unknown. The patient had no other risk factors. The dentist wore gloves and a mask and there was no recognized break in technique in which the dentist's blood was exposed to the patient. Four weeks later a sore throat developed in the patient. Twenty-four months after the procedure the patient had an infection of *Pneumocystis carinii* and was found to be HIV-positive. DNA sequencing was done on both the dentist's virus and the patient's virus. The patterns were not identical, but the molecular epidemiologists concluded that the viruses were closely related.

Currently, no state has a regulation restricting an infected health care worker from doing invasive procedures. On an individual basis, licensing boards have given advice about barrier precautions and surveillance, but have stopped short of recommending that the infected practitioner stop practice. Three surgeons, who continued to operate after they learned they had AIDS, had serologic follow-up of their patients. No suspicion of transmission of the virus to any of their patients was found [14-17].

The problem of what to do (if anything) about the operating privileges of the HIV-infected surgeon is a very complex one. At present, there are no clear guidelines. Hopefully, reasonable recommendations will be forthcoming from the CDC. If not, sooner or later, a legal precedent will be handed down from a court decision. Of interest is a Supreme Court ruling as to what risk is serious enough to justify restrictive regulation: 1 in 1,000 risk of death, serious illness, or disability over a 45-year period (the accepted definition of a working lifetime) [18].

The AIDS epidemic is continuing and is of great concern to the medical profession and the public in general. Emotions and hysteria continue to play a role in decision-making and regulations, but this is gradually decreasing as more knowledge is gained. As individuals, health care workers should develop disciplined habits to protect themselves from the infection, but, at the same time, allow them to continue to care for these patients within the ethical guidelines of the medical profession. Health care institutions, if they have not already done so, should plan ahead and establish guidelines for minimizing risks to patients and their workers. They each should establish systems and protocols for counseling individuals who are involved in HIV–related accidents as a result of carrying out their duties within the institution.

I wish to thank David M. Bell, MD, Chief, AIDS Activity, Hospital Infections Program, Center for Infectious Diseases, CDC, for so graciously sharing his information, reviewing the manuscript, and making valuable suggestions.

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CORRESPONDENCE

Could Glucose-Insulin-Potassium Be Considered Only a Step of a Complete Nutritional Program for Complicated Cardiac Patients?

To the Editor:

In their interesting article, Gradinac and associates [1] noted a direct correlation between glucose-insulin-potassium (GIK) infusion and improvement in the reperfused, failed myocardium after hypothermic ischemia. More recently Moulton and Robinson [2] administered *pre*operatively GIK and low-dose dobutamine (3 to 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in patients in whom postoperative balloon support was predicted, weaning them from cardiopulmonary bypass without difficulty. Although exact metabolic mechanisms are still uncertain and conflicting results reported by the literature must still be evaluated, elevation of cardiac glycogen levels by GIK seems to help these hearts to tolerate longer ischemia.

We share the opinion of these authors, but at the same time we consider the GIK infusion as one step of a complete *peri*operative program of artificial nutrition. In this point of view the cardiac patient would be supported with infusion of various nutrients *before, during,* and *after* operation because of the myocardial metabolic implications of stressed states. Clinical attention should be paid to patients with chronic congestive cardiac failure for their high risk of developing the cardiac cachexia syndromes [3], and to complicated surgical patients [4]. In all these cases, enteral [5] or parenteral nutrition [6] should be performed early to decrease the dramatic effects of surgical hypermetabolism and hypercatabolism.

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Optimal Age for Repair of Aortic Coarctation

To the Editor:

We read with interest the excellent article by Heikkinen and Ala-Kulju [1] describing their experience with Vossschulte's "direct isthmusplastic" operation [2]. This technique was originally devised by Vossschulte for repair of coarctation of the aorta with a short-segment stenosis. We agree with Heikkinen and Ala-Kulju that it should only be performed in adolescents or adults, where the diaphragm of the coarctation has already migrated downstream from its typical position opposite the attachment of the ligamentum arteriosum to the junction of the isthmus and the descending aorta and already has become converted into fibrous tissue [3]. If performed at a young age we anticipate a considerable risk of restenosis due to the coarctogenetic potential of residual ductal tissue in the periductal aorta.

Although the optimal age for surgical correction of coarctation of the aorta has been defined with only limited success, we criticize the statement of Heikkinen and Ala-Kulju that the optimal age for repair of coarctation is before the patient reaches school age. Lawrie and associates [4] showed that residual hypertension is a poor prognostic factor after coarctation repair. Indeed, Nanton and Olley [5] found a much higher incidence of permanent hypertension that was not due to restenosis in patients operated on when older than 4 years of age compared with patients operated on when younger. Although Shinebourne and associates [6] made similar observations, the "break-point" in their series was 1 year of age. Also Campbell and co-workers [7] favored prompt repair of coarctation of the aorta in infancy, irrespective of symptoms. Recently, Sciolaro and colleagues [8] confirmed the increased incidence of persistent hypertension after coarctation repair beyond infancy.

The majority of infants with a preductal subtype of coarctation have a major associated intracardiac defect [6]. As indicated by Sinha and colleagues [9], none of these infants with congestive heart failure survives the first year without surgical correction of at least the coarctation. Therefore, the majority of infants with a preductal subtype of coarctation will be operated on nonelectively during the first year of life. Thus, practically speaking, elective repair mainly applies to the paraductal subtype of coarctation. Because the latter almost invariably consists of short-segment coarctation with a well-developed isthmus, it is well amenable to elective repair at early age, preferably during the second 6 months of life. With resection and end-to-end anastomosis, using microvascular techniques (including 7-0 polypropylene or polydioxanone suture), this can be done with a low rate of restenosis, as indicated by several recent series. Adherence to this strategy avoids the Scylla of slightly increased incidence of recurrent stenosis at the coarctation repair site during the first 3 months of life and the Charybdis of increased incidence of persistent hypertension after coarctation repair beyond infancy.

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Staging Lung Cancer With Computed Tomography

To the Editor:

I found the recent article by Lewis and associates [1] of great interest, and thought it a valuable addition to the literature on this subject. Their results further emphasize the importance of careful intraoperative assessment of the mediastinum at thoracotomy. We [2] have shown that such a dissection (we prefer the term "sampling") will disclose unsuspected nodal metastasis in 25% of thoracotomies, even after careful preoperative staging with computed tomography with or without mediastinal exploration by mediastinoscopy, supplemented by left anterior mediastinoscopy for tumors of the left upper lobe and left main bronchus.

The concordance between the stage derived by computed tomography and that following such a careful intraoperative assessment, 45.4%, should not discourage our radiological colleagues. This figure is remarkably similar to the figure we found, 46.5%, in a recent publication [3] reporting the variance between the T and N stages determined preoperatively, using all investigations including computed tomography with or without mediastinal exploration, and careful intraoperative staging along the lines used by Lewis and associates. These figures should encourage all surgeons to add mediastinal node sampling to their operative routine. The IASLC has recently endorsed this technique as part of its recommendations on "minimal pre-treatment staging," to be published as part of the proceedings of the Bruge Workshop (June 21–27). We surgeons should recognize that thoracotomy is the final staging investigation, before proceeding with the treatment—pulmonary resection.

I would ask Lewis and associates to clarify one point. They found the computed tomographic scan falsely negative in 19 patients, and yet later we were told that mediastinal node deposits were found in 69 patients at thoracotomy. Are we to assume that the other 50 patients proceeded to thoracotomy despite a positive scan? Was this checked preoperatively by mediastinal exploration?

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Reply

To the Editor:

Mediastinal lymph node sampling before resection in lung cancer patients is performed in many centers. Some authors feel that documentation of N2 disease contraindicates potential curative resection. Our center pursues an aggressive approach to stage IIIa patients (enlarged mediastinal lymph nodes by computed tomographic scan) with neoadjuvant chemotherapy followed by exploration [1]. Those patients who cannot be resected for cure are treated by aggressive intraoperative brachytherapy [2]. The additional 50 patients mentioned by Mr Goldstraw were part of this surgical subset.

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Single Drain (Pleura, Pericardium, Mediastinum) After Open Heart Operations

To the Editor:

A fascinating facet of cardiac surgery is the never-ending scope for fresh thinking on "standard" practices. Postoperative chest drainage is an example.

Smulders and associates [1] refer to the high incidence of postoperative pericardial effusion, sometimes leading to tamponade and probably related to ineffective drainage. They accept postoperative pericardial effusion as inevitable in some patients and advocate early removal of the drains because of discomfort, mechanical irritation to the heart and pericardium, and increased risk of infection.

One of our patients who underwent closure of an atrial septal defect proved to have a large congenital pericardial window in the left side. A single pleural drain inserted after opening the left pleural cavity proved effective. This led us to adopt the following procedure as a routine in subsequent patients. A large pericardial window is created by an incision parallel and 1 cm anterior to the right phrenic nerve from the superior to the inferior vena cava. The lower end of the incision is continued forward parallel to the diaphragm for about 3 cm. The pericardium is closed in the midline using three or four interrupted stitches. The right pleura is widely opened. Thus the mediastinum and the pericardial and pleural spaces form a common space that is effectively drained by a single pleural tube. In patients undergoing internal mammary artery grafting, a pericardial window is made behind the left phrenic nerve parallel and close to the diaphragm to avoid herniation of the heart. A left pleural drain is inserted after widely opening the pleura.

Of 130 patients who underwent open heart operations, disruption of the right ventricular outflow patch and possible tamponade developed in only 1; this patient underwent emergency rethoracotomy and was resuscitated. In another patient elective rethoracotomy was done to evacuate clots from the pleural cavity.

This technique has the following advantages. Incidence of tamponade has been negligible (0.8%). Mediastinal or pericardial collection was not seen. Pleural collection occured in 1 patient in whom clots were evacuated by an elective rethoracotomy. There is no risk of mechanical damage to the heart, vessels, bypass grafts, outflow patches, and conduits. A single drain is economical and makes transport and postoperative monitoring of drainage easy. There is no need for hurry to remove the drain. In the rare event of infection, not seen in the present series, an empyema would result, which can be easily corrected compared with the dreaded mediastinitis or pericarditis.

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Reply

To the Editor:

The Madras group describes an alternative for drainage of the pericardial space after cardiac operations with—at least in their patients—a low incidence of cardiac tamponade.

In our practice a rethoracotomy has to be performed in approximately 4% of patients owing to hemorrhage, but in only a minority of these patients is tamponade apparent as well. In case of hemorrhage our policy is to reopen the sternal wound when blood loss exceeds 200 mL/h in the first 3 hours after operation or 100 mL/h in the following period. When hemodynamic signs suggesting tamponade without extensive drain production are present, a prompt transesophageal echocardiogram is done to estimate the presence or absence of intrapericardial fluid. With a positive diagnosis or in case of doubt, an immediate rethoracotomy is carried out.

It is surprising how little negative influence postoperative hemorrhage has on short-term and long-term postoperative course and mortality when patients are treated in this way.

In our opinion, routine opening of the pleural space(s) as proposed by Victor and Kabeer carries serious disadvantages. These include the necessity to place an intercostal drain causing pain during respiratory movements, which can result in hampering of gas exchange and development of atelectasis. Also, the lateral position of the drain forces the patient not to lie on the ipsilateral side, which can lead to sleeping disorders. In case of a later operation on the lung, adhesions can complicate the intervention considerably. Finally, fluid retention can produce atelectasis and empyema in the early postoperative phase. Eventually, formation of extensive fibrous tissue may develop.

Therefore, in our routine we try to keep the pleural cavities closed whenever possible, even in those patients in whom the mammary artery is dissected free. Proper placement of the drains located in the retrosternal area and in the pericardial space avoids mechanical damage to the heart, great vessels, and freshly placed grafts.

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Congenital Bronchoesophageal Fistula

To the Editor:

We were most interested in the recent article on congenital bronchoesophageal fistulas by Dr W. Risher and colleagues [1], but would perhaps take issue with the penultimate paragraph on the therapy of this problem.

We have treated a patient with congenital bronchoesophageal fistula to the bronchus intermedius by the local application of sodium hydroxide and acetic acid to both bronchial and esophageal aspects of the fistula. This produced most satisfactory results, and 2 years later the patient is well with no symptoms.

Although not in any way critical of Dr Risher and associates' excellent paper, we would simply add that this effective local treatment exists as an option in the occasional patient who is unfit for, or indeed declines, definitive operation for his or her bronchoesophageal fistula.

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1. Risher WH, Arensman RM, Ochsner JL. Congenital bronchoesophageal fistula. Ann Thorac Surg 1990;49:500-5.

Reply

To the Editor:

We appreciate the letter of Parry and Juma in which they report closure of a congenital bronchoesophageal fistula with sodium hydroxide and acetic acid. Unfortunately, this technique has not been reported previously; hence, we were unable to give credit to them.

We believe that their treatment is a good option, particularly for those patients who decline operation or are too sick to undergo surgical resection. However, it is imperative that a precise diagnosis of *congenital* bronchoesophageal fistula be determined before the application of their treatment and that there be no question of malignancy or necessity of resection of permanently damaged lung tissue.

Again, we are happy to learn of this optional modality in the treatment of congenital bronchoesophageal fistulas.

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Uncomfortable Issues

To the Editor:

The recent editorial by Dr Edmunds [1] commenting on a paper by Deleuze and co-workers [2] touches on some points that so far have been avoided in the scientific literature. Although several reports have appeared in the literature claiming satisfactory results, especially with valve replacement in geriatric populations, one has to suspect careful case selection is leading to these results. We all agree that the patient's biologic age rather than the chronologic age determines the outcome. Thus, the question arises what determines biologic age? The more senior among us will say experience. Yet there is very little objective data available to answer this question.

The Veterans Administration Preoperative Risk Assessment Study [3] and the New York State Department of Health Report [4] are two recent attempts at shedding some light in a nonbiased fashion (reporting of all cardiac cases is mandatory for both studies). I am not aware of any randomized study comparing total expenditure, quality of life, and longevity in operated versus nonoperated geriatric patients. More and more frequently during a conflict of interests, an ethics committee makes decisions in this age group, often with inadequate data.

Because cardiac surgery in this country is under increasing scrutiny by the public and its representatives, it would seem clearly advantageous for the cardiac surgical community to establish some guidelines for dealing with geriatric patients, before having arbitrary rules imposed by in-patient third-party payers and governmental agencies. I wonder if Dr Edmunds could give us his guidelines about operability in this patient group and tell how he handles disagreements between the family, the referring cardiologist, and the surgeon.

Thomas V. Bilfinger, MD

Department of Surgery HSC T 19-080
University Hospital Stony Brook
Stony Brook, NY 11794

References

1. Edmunds LH. Uncomfortable issues. Ann Thorac Surg 1990;50:173–4.
2. Deleuze P, Loisauce DY, Besnainou P, et al. Severe aortic stenosis in octogenarians: is operation an acceptable alternative? Ann Thorac Surg 1990;50:226–9.
3. Grover FL, Hammermeister KE, Buchfiel C, et al. Initial report of the Veterans Administration Preoperative Risk Assessment Study for Cardiac Surgery. Ann Thorac Surg 1990;50:12–28.
4. New York State Department of Health. Adult open heart surgery in New York state: an analysis of risk factors and hospital mortality rates. Bureau of Health Care Research and Information, 1989.

Reply

To the Editor:

For the first time in the history of mankind, substantial numbers have achieved advanced age. Life expectancy has nearly doubled in the 20th century, but unfortunately the prevalence of cardiovascular disease increases with age. Our unprecedented longevity raises new medical, economic, and ethical issues for which we are unprepared. A politically sensitive Congress wants the medical profession to devise methods to provide satisfactory care (as judged by voters) at affordable cost. Doctors, as advocates of individual patients, are unable to ration or restrict care and are further compromised by the economic temptations of our traditional prescriber-provider system. Dr Bilfinger, and undoubtedly other pressed professionals and concerned laymen, want "guidelines for dealing with geriatric patients."

It is easy to construct "guidelines" for unknown persons; it is not so easy to apply restrictive guidelines to family and personal patients. Effective, expensive treatments for geriatric heart disease do exist; it is unlikely that members of a representative government can selectively deny these treatments to specific subsets of the population or that the judicial system will uphold any discriminatory legislation.

Assembly of a database using standard definitions for various descriptors (eg, "hospital mortality") is an important first step toward solution or resolution. Careful analysis of nonselected, unbiased data can identify independent incremental risk factors for operative mortality and morbidity. These data provide a means to quantitatively estimate risks, benefits, and costs of operations for individual patients and provide a basis for a decision to operate or not operate. These estimates enable patients and families to participate in the decision; governments and other insurers can use the data to apportion costs; regulators obtain a means to monitor quality of care; and doctors and legislators duck the issue by shifting decisions to individual patients. Who is more qualified to make life and death decisions than the patient himself or herself?

What are my guidelines in our present state of ignorance? First I assess the independent incremental risk factors for early death and permanent morbidity (eg, stroke, permanent dialysis) using the Parsonnet additive model [1] and my experience [2] to estimate risk. Then I personally present the data to the patient and available children. I present both the benefits that the magic of successful heart surgery produces and the risks and suffering connected with operation. I present the risk numerically as the "percent chance" of a bad result (eg, death, stroke). We often review alternatives, which usually have been exhausted by the time I am consulted. A few patients decide against operation; many defer operation but many of these eventually have operations weeks or months later; perhaps the majority request operation. Success needs no balm; when my operation fails, my conscience is quiet.

L. Henry Edmunds, Jr, MD

Department of Surgery
University of Pennsylvania School of Medicine
3400 Spruce St
Philadelphia, PA 19104

References

1. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989;79(Suppl 1):3–12.

2. Edmunds LH Jr, Stephenson LW, Edie RN, Ratcliffe MB. Open heart surgery in octogenarians. N Engl J Med 1988;319: 131–6.

Coronary Artery Bypass Grafting in Patients With Calcified Aorta

To the Editor:

In a recent report published in *The Annals* [1], Dr Suma has described a method of coronary artery bypass grafting in patients with calcified ascending aorta.

Of the 1,200 coronary artery bypass procedures performed in the last 1½ years, we have come across 3 patients with calcified atherosclerotic aorta. One of the patients was managed using a method similar to what Dr Suma has described as the "aortic no-touch technique." In the remaining 2 patients our management was different. Both the patients were women aged 65 and 67 years. They had small atherosclerosed femoral arteries, and hence cardiopulmonary bypass could not be instituted. We therefore did myocardial revascularization without cardiopulmonary bypass.

In 1 patient with left main stem disease, we did left internal mammary artery to left anterior descending artery grafting. It was not possible to graft the circumflex artery (which was small) through a median sternotomy without cardiopulmonary bypass. In the second patient with double-vessel disease, right internal mammary artery was used to bypass right coronary artery, and saphenous vein graft was anastomosed with the left anterior descending coronary artery. Right internal mammary artery formed the site of proximal anastomosis for the saphenous vein graft.

All 3 patients survived with relief of angina and had no complications such as cerebrovascular accidents or perioperative myocardial infarction.

S. S. Arsiwala, MCh
H. S. Bedi, MCh
V. K. Sharma, MCh
N. Trehan, MD

Escorts Heart Institute and Research Centre
Okhla Rd
New Delhi 110 025
India

Reference

1. Suma H. Coronary artery bypass grafting in patients with calcified ascending aorta: aortic no-touch technique. Ann Thorac Surg 1989;48:728–30.

Reply

To the Editor:

With the increasing incidence among elderly patients of ischemic heart disease, atherosclerotic ascending aorta and related cerebrovascular accidents have become a major concern in coronary artery bypass grafting. Dr Arsiwala and colleagues successfully managed this kind of patient using the aortic no-touch technique with and without cardiopulmonary bypass. Aortic no-touch technique with cardiopulmonary bypass is safe and effective as I have previously reported [1]. Although use of in situ arterial graft is essential for this procedure, proximal anastomosis to the ascending aorta can be performed relatively safely under hypothermic circulatory arrest when the vein graft is necessary. Soft and thin parts of the ascending aorta are easily detectable under circulatory arrest. The ascending aorta should be incised without punch-out in such cases, and vein graft can be anastomosed with continuous suture in about 5 minutes under circulatory arrest. I currently am using circulatory arrest for the anastomosis of the internal thoracic artery to the circumflex artery and for anastomosis of the vein graft to the ascending aorta in patients with severe atherosclerotic ascending aorta.

Coronary artery bypass grafting without cardiopulmonary bypass is a different situation. Right coronary artery proximal to the posterior descending artery bifurcation can generally easily be bypassed under the beating heart. With the circumflex artery, on the other hand, it is quite difficult and dangerous to do so through a median sternotomy because retraction of the heart provokes massive aortic regurgitation. Now, what about the anterior descending artery? I have experienced a few cases of vein graft anastomosis to the left anterior descending artery under the beating heart but with cardiopulmonary bypass after unsuccessful internal thoracic artery anastomosis. There are two problems that I can point out about this technique. First, exposure of the left anterior descending artery is more difficult than with a fibrillated or arrested heart when the artery is covered with adipose tissue. Second, meticulous anastomosis is possible in case of impaired left ventricular function, but sutures may not be properly placed and anastomotic leakage or stenosis is more likely to occur when the left ventricle has vigorous motion. Therefore, use of internal thoracic artery is dangerous in such a situation.

The number of patients who require avoidance of manipulation of the ascending aorta is increasing. We must establish a systematic evaluation method to detect the atherosclerotic change of the ascending aorta before and during operation and a refined surgical technique should be considered to handle it.

I congratulate Dr Arsiwala and colleagues for their interesting case report and their skilled hands.

Hisayoshi Suma, MD

Department of Cardiovascular Surgery
Mitsui Memorial Hospital
1 Kanda Izumicho Chiyodaku
Tokyo 101
Japan

Reference

1. Suma H. Coronary artery bypass grafting in patients with calcified ascending aorta: aortic no-touch technique. Ann Thorac Surg 1989;48:728–30.

1990 Meeting
Southern Thoracic Surgical Association

The Thirty-seventh Annual Meeting of the Southern Thoracic Surgical Association was held at the Hyatt Regency Cerromar Beach, Dorado, Puerto Rico, November 8–10, 1990. The President was Harvey W. Bender, Jr, MD. Officers elected for the coming year are: *President,* Robert M. Sade, MD; *President-Elect,* William A. Cook, MD; *Vice President,* Hooshang Bolooki, MD; and *Secretary-Treasurer,* Hendrick B. Barner, MD.

The following applicants were elected to membership:

Glenn R. Barnhart, MD
Norfolk, VA

Kenneth M. Begelman, MD
Boca Raton, FL

Harry G. Burton III, MD
Asheville, NC

Stephen J. Dewan, MD
Austin, TX

Michael L. Edwards, MD
Charleston, SC

David L. Galbut, MD
Miami, FL

Richard F. Heitmiller, MD
Baltimore, MD

Richard W. Hoefer, MD
Sarasota, FL

Michael D. Horowitz, MD
Miami, FL

Alan M. Johnson, MD
Asheville, NC

Kirk R. Kanter, MD
Atlanta, GA

James R. Kauten, MD
Atlanta, GA

James Michael Kirby, MD
Bryan, TX

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Alexandria, LA

Neal David Kon, MD
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Bruce D. Walley, MD
Winston-Salem, NC

David Christopher Wells, MD
Roanoke, VA

Walter George Wolfe, MD
Durham, NC

Richard W. Zollinger II, MD
Charlotte, NC

Elevated to senior membership were: Robert L. Anderson, MD, R. Adams Cowley, MD, Kenneth Cruze, MD, David P. Hall, MD, John R. Hankins, MD, Jackson Harris, MD, Richard E. Hughes, MD, Cary J. Lambert, MD, Joseph R. Lancaster, MD, Lawrence S. McGee, MD, William F. Simpson, MD, Kenneth R. T. Tyson, MD, and Don C. Wukasch, MD.

The President's Award for the best scientific paper given at the 1989 meeting was presented to Harvey Pass, MD, Mark Stovroff, MD, John Vetto, MD, John Doppman, MD, Lynnette Nieman, MD, and Gordon Cutler, MD, for their paper "Management of Patients With Thoracic Ectopic ACTH Syndrome."

The 1991 meeting will be held at the Hyatt Regency Grand Cypress, Orlando, Florida, November 7–9, 1991. Chairman of the Program Committee will be Frederick L. Grover, MD, Chairman of the Postgraduate Committee will be William A. Baumgartner, MD, and Chairman of the Membership Committee will be F. Hammond Cole, Jr, MD.

Hendrick B. Barner, MD
Secretary-Treasurer
Southern Thoracic Surgical Association
401 N Michigan Ave
Chicago, IL 60611-4267

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The European Association for Cardio-Thoracic Surgery
Notice of Annual Meeting

The Fifth Annual Meeting of the European Association for Cardio-Thoracic Surgery will be held September 22–25, 1991, at the Royal Lancaster Hotel in London, United Kingdom. The scientific sessions are open to all registered participants. The registration fee includes admission to the entire scientific program, meeting documentation, welcome reception on Sunday evening, concert on Monday evening, and tea and coffee.

Registration and Hotel Reservation

All participants of the meeting should request a registration form from Conference Associates & Services Ltd, EACTS, Congress House, 55 New Cavendish St, London W1M 7RE, United Kingdom (telephone: 071 486 0531; facsimile: 071 935 7559).

Scientific Program

Scientific papers will be considered from members and nonmembers. Member sponsorship is not necessary. The abstract reproduction form is mandatory for submission of abstracts and can be obtained either through the Conference Secretariat or from the Scientific Secretariat of EACTS. Authors are requested to follow carefully the instructions outlined on the abstract form. Each abstract must be accompanied by ten photocopies without indication of authors and institution. Deadline for submission of abstracts is March 1, 1991. A letter of confirmation will be sent to the authors after receipt of the abstract by the Secretary General of EACTS. The decision of the Program Committee will be mailed to authors in May 1991. Papers accepted for presentation at the meeting will be published, subject to editorial review, in the *European Journal of Cardio-Thoracic Surgery*. At the time of presentation, the manuscript and two copies must be handed over to the editorial desk at the conference.

The body of the abstract should accurately describe the completed work. Unless specified otherwise, the first-named author will receive the correspondence and is expected to give a 10-minute presentation of the paper and conduct the discussion. Abstracts must represent unpublished work, not previously presented at a major scientific meeting. Instructions and Abstract and Transmittal Forms are available from Prof M. Turina, Scientific Secretariat EACTS, Clinic for Cardiovascular Surgery, University Hospital, CH-8091 Zürich, Switzerland (telephone: 1 255 20 39/1 255 32 98; facsimile: 1 255 44 46).

Industrial Exhibition

The industrial exhibition will be organized at the congress venue. The applications for exhibition space should be addressed to Conference Associates and Services Ltd, EACTS, Congress House, 55 New Cavendish St, London W1M 7RE, United Kingdom.

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THE
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and the Southern Thoracic Surgical Association*

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information.

Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Fortieth Annual Meeting of the American College of Cardiology, Atlanta, Georgia—March 3–7, 1991

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

First International Symposium on Diseases of the Aorta, Tokyo, Japan—March 6–8, 1991

For information on this meeting, contact Secretariat of ISDA, c/o Japan Convention Services, Inc, Nippon Press Center Bldg, 2-2-1, Uchisaiwai-cho, Chiyoda-ku, Tokyo 100, Japan.

Arrhythmia Surgery Operative Clinics, St. Louis, Missouri—March 21–23, 1991, and October 3–5, 1991

For information on these meetings, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

Neonatal Cardiac Surgery for Transposition of the Great Arteries, Plessis-Robinson, France—March 24–28, 1991

For information on this meeting, contact Aloma Wybenga, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

General Thoracic Surgery, Boston, Massachusetts—April 22–23, 1991

For information on this meeting, contact the Department of Continuing Education, Harvard Medical School, PO Box 825, Boston, MA 02117; or telephone (617) 432-1525.

Myocardial Assist Techniques Seminar I, Washington, DC—May 2–3, 1991

For information on this meeting, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

Second Scientific Meeting of the International Association for Cardiac Biological Implants, Washington, DC—May 5, 1991

The topic of this meeting, dedicated in memory of the late Donald Magilligan, MD, will be infective endocarditis of heart valves. For information on this meeting, contact Dr Shlomo Gabbay, Office of the Secretary, UMDNJ, Department of Surgery, Room G502, 100 Bergen St, Newark, NJ 07103.

Seventy-first Annual Meeting of The American Association for Thoracic Surgery, Washington, DC—May 6–8, 1991

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Quality of Life After Open Heart Surgery, Antwerp, Belgium—May 16–18, 1991

This meeting is sponsored by The World Health Organization, the European Society of Cardiology, and the International Society and Federation of Cardiology. For information on this meeting, contact P. J. Walter, MD, FACS, Professor and Chairman of the Department of Cardiovascular Surgery, University Clinic of Antwerp, B 2520 Antwerp, Wilrijkstraat 10, Belgium; or telephone 00323.829.11.11 (facsimile: 00323.830.20.99).

Ann Thorac Surg 1991;51:A-29–30

Vascular Surgery 1991—Current State of the Art, New York, New York—May 16–18, 1991

For information on this meeting, contact Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042; or telephone (718) 470-8650.

Coronary Surgery: Clinical and Basic Perspectives, Sheffield, England—May 17, 1991

For information on this meeting, contact G. D. Angelini, Clinical Sciences Centre, Northern General Hospital, Herries Rd, Sheffield S5 7AU, England.

Surgery for Coronary Artery Disease, Durham, North Carolina—May 20–21, 1991

For information on this meeting, contact Vanessa Moore, PO Box 2986, Duke University Medical Center, Durham, NC 27710, or telephone (919) 684-6077; or contact American College of Cardiology, Extramural Programs Department, 9111 Old Georgetown Rd, Bethesda, MD 20814, or telephone (800) 253-4636.

Fourth International Symposium on Echocardiography and Doppler in Cardiac Surgery, Innsbruck, Austria—May 27–29, 1991

For information on this meeting, contact G. Maurer, MD, or W. Mohl, MD, PhD, c/o Interconvention, A-1450 Vienna, Austria; or telephone +43/1/23 69/2642 (telex: 11 18 03; facsimile: +43/1/23 69/648).

Ninth World Symposium on Cardiac Pacing and Electrophysiology, Washington, DC—May 28–31, 1991

This meeting will incorporate the Twelfth Annual Scientific Session of the North American Society of Pacing and Electrophysiology. For information on this meeting, contact IXth World Symposium Secretariat, c/o NASPE, 377J Elliot St, Newton Upper Falls, MA 02164; or telephone (617) 237-1866 (facsimile: (617) 431-1991).

The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Boston, Massachusetts—June 3–5, 1991

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Cardiac Arrhythmia Surgery International Seminar II, Geneva, Switzerland—June 12–14, 1991

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

Seventeenth Annual Meeting of The Western Thoracic Surgical Association, Seattle, Washington—June 26–29, 1991

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Techniques in Pulmonary and Oesophageal Surgery, Liverpool, England—July 14–16, 1991

For information on this meeting, contact Mr R. J. Donnelly, The Cardiothoracic Centre, Broadgreen Hospital, Thomas Dr, Liverpool L14 3LB, England; or telephone 051 228 4878 (facsimile: 051 220 8573).

Twentieth World Congress of The International Society for Cardiovascular Surgery, Amsterdam, the Netherlands—September 1–6, 1991

For information on this meeting, contact the Registrar: XX World Congress—ISCVS, International Travel Service, Inc, 104 Wilmot Rd, Suite 300, PO Box 825, Deerfield, IL 60015; or telephone (708) 940-2100 (facsimile: (708) 940-2386); or contact the Congress Secretariat, International Society for Cardiovascular Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Current Issues in Thoracic Organ Transplantation, Essen, Germany—September 19–21, 1991

For information on this meeting, contact Organizing Secretariat, Gisa Brodde Meetings, Saalbau Essen, PO Box 100301, D-4300 Essen 1, Germany; or telephone (0)201-232121 (facsimile: (0)201-232273).

Heart Valve Replacement—Past Performance: Future Prospects, Sheffield, United Kingdom—September 19–21, 1991

For information on this meeting, contact Jenny Pupius, Symposium Secretariat, Department of Medical Physics and Clinical Engineering, Royal Hallamshire Hospital, Glossop Rd, Sheffield S10 2JF, United Kingdom; or telephone (0742) 555250 (facsimile: (0742) 729981).

Fifth Annual Meeting, European Association for Cardio-Thoracic Surgery, London, United Kingdom—September 22–25, 1991

For information on this meeting, contact Organising Secretariat, Conference Associates & Services, Ltd, Congress House, 55 New Cavendish St, London W1M 7RE United Kingdom; or telephone 071 486 0531 (facsimile: 071 935 7559; telex: 934 346 CONFAS G).

Fifth Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Alexandria, Egypt—September 23–27, 1991

For information on this meeting, contact Prof M. El-Fiky, Chairman, Cardiac Surgery Department, Ain Shams Faculty of Medicine, Abbassia, Cairo, Egypt; or telephone (202) 834981 or (202) 835495 (facsimile: (202) 834981).

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Arthur Carlucci, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010 (telephone: (212) 633-3806; facsimile: (212) 633-3880). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.25 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $17.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3853). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad. To respond to an anonymous ad, write to Box Number, *The Annals of Thoracic Surgery*, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

SITUATIONS AVAILABLE

Cardiothoracic surgeon, ABTS certified/eligible, with primary interest in cardiac surgery, wanted immediately to replace member of established surgical group practicing in Allentown, PA. Competitive salary/fringe benefits. Position leads to partnership for successful candidate.

Please send curriculum vitae, clinical experience, and references to Joan M. Persa, Administrator, 1275 South Cedarcrest Blvd, Allentown, PA 18103; (215) 821-8790. 393I/B

Cardiovascular and thoracic surgeon: BE/BC wanted to join well-established private group practice in Philadelphia area. Seek recent or upcoming graduate. Please send curriculum vitae.

Please respond to Box 394. 394I/B

Cardiovascular surgeon to become second surgeon in new (two year old) adult cardiac program on west coast of Florida.

Submit CV to Manatee Cardiac Surgeons, PA, 201 4th Ave East #2, Bradenton, FL 34208. 396I/B

Cardiovascular surgeon, board certified/eligible, wanted to join two surgeons in an established cardiovascular program in the southeastern USA. Must have experience in adult cardiac, thoracic, and vascular surgical procedures. Salary/full partnership negotiable. Please send resume.

Please respond to Box 398. 398I/B

Thoracic/vascular surgeon needed to join prominent, active 3-man group in desirable suburban community in greater NY metropolitan area. Excellent opportunity for well-trained, highly motivated individual. Recent graduate preferred. Possible academic affiliation. Please respond with CV.

Please respond to Box 404. 404J/C

Thoracic and cardiovascular surgeon, board certified or eligible, wanted for an established practice in the Midwest with experience in adult cardiac, thoracic, and peripheral vascular surgery. Experience or training in heart/lung transplantation preferred. Initial contact should include curriculum vitae, clinical experience, and names of references.

Please respond to Box 408. 408J/B

Cardiac surgeon—board certified/eligible to be third member of established practice in suburb of Washington, DC, expanding to second hospital. Excellent compensation and benefits. Great opportunity for recent graduate wishing to locate in area of nation's capital. Practice focus is primarily in adult cardiac surgery with additional work in thoracic and peripheral vascular surgery available.

Please send curriculum vitae to PO Box 34945, Bethesda, MD 20817. 415J/C

Cardiothoracic/vascular surgeon: board certified in general and thoracic surgery. Minimum of 2 years of practice experience. Very active private multispecialty practice. Located in western Pennsylvania. Salary leading to full partnership. Excellent benefits. Detailed CV must accompany response. All replies treated confidentially.

Please respond to Box 419. 419J/C

Cardiothoracic surgeon needed to join established 2-man group in practice of adult cardiac, pulmonary, and vascular surgery. Must be board certified or eligible and graduate from a US medical school.

Please respond to R. W. Ruess, MD, 1834 Broadway, Cape Girardeau, MO 63701. 422J/C

Cardiovascular-thoracic surgeon—BE/BC to join established and growing 2-surgeon group in northeastern US. Practice includes high volume cardiac and general thoracic surgery. Recent trainee preferred. Submit CV.

Please reply to Box 423. 423J/C

Pacific Northwest opportunity for cardiothoracic surgeon with 2 to 4 years of experience. Growing multispecialty group practice in Portland, Oregon, seeks dynamic surgeon to join 3 other surgeons in our practice. General thoracic and vascular experience necessary.

Please send curriculum vitae to Dr James W. Asaph, MD, 507 NE 47th Ave, Portland, OR 97213-2282. 426K/D

Cardiac surgeon wanted to join established private practice in upstate New York, primarily adult cardiac. Board certified or eligible required. New or recent graduate preferred. Please send CV and references.

Please respond to M. A. Marvasti, MD, 101 Union Ave, #813, Syracuse, NY 13203. 429K/D

Wanted: BE/BC general surgeon with interest and experience in thoracic surgery who enjoys general surgery, or non-cardiac thoracic surgery, to assume practice of retiring double-boarded thoracic/general surgeon. 34-member multispecialty group in dynamic area hub city of 35,000, with six satellite offices in strategic locations and referral area of 300,000 plus. Superb hospital facilities, including CT, MRI, cardiac surgery, neurosurgery, etc. Directed towards those concerned about quality family lifestyle and professional concerns.

Contact Recruitment Coordinator, Park Clinic, 890 North Eisenhower Ave, Mason City, IA 50401; or dial 800-798-4321 for more information. 431K/D

Cardiovascular/vascular surgeon wanted to join busy established adult practice in Ohio. Recent graduate preferred. Please submit curriculum vitae. Association will lead to partnership.

Please respond to Box 436. 436K/C

BC/BE adult cardiothoracic surgeon wanted to join active established department in large multispecialty group practice located in metropolitan Midwest community. Medical school affiliation available. Respond with curriculum vitae.

Please respond to Box 437. 437K/D

Minneapolis cardiothoracic/vascular group seeks to add fifth surgeon, BC/BE.

Respond to BLH Physician Search, 2231 Lee Ave N, Minneapolis, MN 55422; (612) 588-1116 or -0333. 438L/E

Board certified/eligible cardiothoracic surgeon for busy 1-physician practice in Atlanta. Transplant experience. Future partnership.

Send resume to Georgia Cardiac Surgical Association, PO Box 491203, College Park, GA 30349. 439L/E

Thoracic surgeon, BE/BC, wanted to join 4-man group on Gulf Coast of Florida, specializing in general, vascular, and noncardiac thoracic surgery. Recent graduate preferred. Please send CV and references.

Please respond to Box 441. 441L/B

Cardiothoracic surgeon wanted for July 1991: expanding private practice in Philadelphia. Adult cardiac and thoracic surgery. Academic appointment. Eventual partnership.

Send CV and references to PO Box 1295, Philadelphia, PA 19105. 442L/B

Wanted—thoracic surgeon, BE/BC, to join a board certified surgeon for noncardiac thoracic surgery and peripheral vascular surgery in a growing medical center in upstate New York.

Please respond to Box 451. 451L/B

Chief, Cardiothoracic Surgery: Excellent opportunity to lead cardiothoracic surgery department for 400-bed community teaching hospital located in western Pennsylvania. This dynamic facility performs 900 open heart procedures and 5,600 catheterizations per year. Qualified candidates should possess academic credentials and have interest in developing clinical research.

Please contact Jeanne Dowrick, Fulton, Longshore and Associates, Inc, 527 Plymouth Rd, Plymouth Meeting, PA 19462; telephone (800) 346-8397 or (215) 834-6780. 453L/B

Thoracic and vascular surgeon needed—Southeast: Looking for a partner to join an established surgeon to practice noncardiac thoracic and vascular surgery in mid-sized city. Must be board certified or eligible. No buy-in needed, guaranteed income available. Excellent community to raise a family with the cultural advantages of a large city but not the hassles. Will consider others, but recent graduate preferred. Send CV, and include description of interests, and career goals.

Please respond to Box 454. 454L/C

Cardiovascular and thoracic surgeon: Position available for a board certified or eligible cardiovascular and thoracic surgeon to join a 2-man private practice involved with adult cardiac, thoracic, and peripheral vascular surgery in a desirable eastern metropolitan area. Association features competitive salary, excellent fringe benefits, and a goal of early partnership. Please send curriculum vitae.

Please respond to Box 455. 455L/B

Surgeon with interest/experience in hemodialysis access to manage 400–450 cases per year as part of a large, established, mid-Atlantic cardiovascular and thoracic surgical practice. ABS required; salary, incentives, and call schedule negotiable. Send CV.

Please respond to Box 456. 456L/B

Cardiothoracic surgeon interested in joining an established practice in the Southwest. Must be experienced in adult cardiac, pulmonary, and vascular surgery. Must be board certified/board eligible. Please respond with curriculum vitae.

Please respond to Box 457. 457L/C

Thoracic and cardiovascular surgeon wanted to join a busy practice. Prefer recent graduate. Must be board certified or eligible. Located in Midwest. Please respond with curriculum vitae.

Please respond to Box 458. 458L/B

Cardiovascular and thoracic surgeon, BE/BC, to join another physician in a rapidly expanding private practice located in the Southeast. Please send curriculum vitae and references.

Please respond to Box 459. 459L/E

University of Massachusetts Medical Center is recruiting candidates for its newly opened Cardiothoracic Surgical Residency Program for 1991, 1992, and 1993. The applications for the 1993 position will be processed through the Match Program for Cardiothoracic Residencies.

Request applications from and submit curriculum vitae and three letters of recommendation to Thomas J. Vander Salm, MD, Chief, Division of Cardiothoracic Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655; telephone: (508) 856-2216. 462L/E

Cardiovascular surgeon to join another physician in partnership. Lucrative practice opportunity. *Must do* comprehensive cardiovascular *and* thoracic procedures. On staff at five major hospitals. Two offices and staff in place. Must be able to establish new lines of referral. State-of-the-art pacemaker clinic in office. Suburban location near Chicago, IL (population of 5 million) is 25 minutes due west of downtown. $175,000 first year salary plus pension, buy-in, and other benefits.

Send CV or call David Cornett, Jackson and Coker, Inc, 115 Perimeter Center Place, Suite 380 10031, Atlanta, GA 30346; telephone: 1-800-544-1987. 467A/C

Assistant/Associate Professor needed for expanding *cardiothoracic surgery* program. Position involves primarily adult cardiac surgery with some thoracic. Experience/interest in electrophysiology advantageous. Commitment to research and teaching essential. Exceptional opportunity for academic development in a desirable community. USF is an EEO/AA employer.

Please send CV to Peter P. McKeown, Chief of Cardiovascular & Thoracic Surgery, University of South Florida, #730, 4 Columbia Dr, Tampa, FL 33606. 469A/C

Cardiac surgeon, board certified. Minimum 5 years experience in adult cardiac surgery to join 2-surgeon practice in Southeast. Send CV.

Please respond to Box 471. 471A/C

Assistant surgeon sought for busy adult cardiothoracic surgery practice. Entire responsibility will be to assist four senior surgeons in the operating room. Board certification or eligibility in general surgery, and some experience in vascular and/or thoracic surgery, desirable. Must be licensed in Pennsylvania or able to obtain license. Generous salary and fringes. Position is available immediately and could be permanent. Ideal location in very pleasant, small city near major eastern metropolitan centers.

Please respond with CV to Lawrence I. Bonchek, MD, 555 North Duke St, Lancaster, PA 17603; (717) 295-8395. 472A/B

Cardiothoracic surgeon, board eligible/board certified, to join expanding academic practice at The Medical College of Pennsylvania. Excellent clinical and investigational facilities available with ample opportunities for clinical or basic science research. Solid general surgery residency with active medical student participation. Practice includes valve repairs, electrophysiologic surgery, transplantation. Salary very competitive.

Please send curriculum vitae to Glenn Whitman, MD, The Medical College of Pennsylvania, 3300 Henry Ave, Philadelphia, PA 19129 or call (215) 842-6564. 476A/B

Cardiothoracic/vascular surgeon, BE/BC, wanted to join growing practice in New Jersey. Recent graduate preferred. Please respond with CV.

Please respond to Box 477. 477A/C

Cardiovascular thoracic surgeon—board certified/board eligible and recently trained to join an established, busy, dynamic, and expanding private practice in northwest Indiana. The sphere of practice is approximately 30 minutes from downtown Chicago. Guaranteed excellent starting salary with progressive future growth and comprehensive corporate fringe benefit program.

Write including CV and details of experience and capabilities to PO Box 3066, Munster, IN 46321. 478A/B

Thoracic and vascular surgeon, board certified, to join active (noncardiac) thoracic and vascular practice in northern New Jersey. Competitive salary and benefits. Please respond with curriculum vitae.

Please respond to Box 481. 481A/C

Cardiothoracic surgeon, BC/BE, to join an extremely busy and rapidly expanding solo practice of predominately adult cardiac surgery in a medium-size southern city serving as a regional referral center. Unusually high quality medical care in this outstanding community. Excellent opportunity for a new or recent graduate with generous compensation package leading to early partnership. Please send CV.

Please respond to Box 482. 482A/C

Cardiovascular and thoracic surgeon, BE/BC, wanted to join a busy private practice in Pittsburgh, PA. Please respond with curriculum vitae and details of experience.

Please respond to Box 483. 483A/C

Cardiothoracic surgeon, BE/BC, to join busy 1-man private practice in Dallas. Excellent opportunity. Salary leading to partnership. Please send CV and references.

Respond to Practice Enhancement Resources, PO Box 655999, Dallas, TX 75265; Attention: Carol. 487B/D

Pacific Northwest—Adult cardiothoracic surgeon, board certified, to join established surgeon in growing private practice. Quality medicine in an outstanding area. Early full partnership.

Please respond to Box 488. 488B/C

Cardiovascular and thoracic surgeon to join established 3-man private practice in mid-South. Practice includes thoracic, cardiac, and vascular surgery. Must be board certified or eligible in thoracic and cardiovascular surgery. Prefer candidate who has recently completed his/her training. Please respond with curriculum vitae.

Please respond to Box 489. 489B/G

A busy greater Boston cardiothoracic surgical group seeks to add a third surgeon as soon as possible. This practice operates from a multihospital referral base. Candidate must be BE/BC. Excellent salary and benefit package. Please respond with CV.

Please respond to Box 490. 490B/D

Cardiovascular/thoracic surgeon wanted to join principal in metropolitan city on west coast of Florida. Must be ABTS certified or eligible and hold Florida license. Good opportunity for young, aggressive, energetic individual. Experience in cardiac transplantation an asset.

Please respond to Box 491. 491B,D,F

Emory University is seeking applicants for faculty position in Cardiothoracic Surgery as Assistant Professor. Applicants should have demonstrated productivity in surgical research and be technically strong in all phases of adult cardiac surgery.

Submit curriculum vitae and letters of recommendation to Robert A. Guyton, MD, Chief, Cardiothoracic Surgery, 1365 Clifton Rd NE, Atlanta, GA 30322. Emory University is an affirmative action/equal opportunity employer. 492B

Faculty/academic position: The Division of Cardiothoracic Surgery, University of Washington, is seeking a BC/BE adult cardiothoracic surgeon. The individual will have a dual appointment at University Medical Center and the Veterans Administration Medical Center. He/She will be responsible in establishing the VA clinical, education, and research program. He/She should have demonstrated a strong clinical cardiac and thoracic surgery background and commitment to education and research. AA/EOE.

Send complete curriculum vitae to Edward D. Verrier, MD, Division of Cardiothoracic Surgery, RF-25, University of Washington, Seattle, WA 98195. 493B

Vacancy exists for a BE/BC thoracic and cardiovascular surgeon. Candidate must have proven clinical and laboratory abilities and vascular surgery fellowship. Training required in major complex vascular procedures.

Please forward curriculum vitae to VAMC. Attention: Carolyn G. Gray, 2002 Holcombe Blvd, Houston, TX 77030; or call (713) 795-7463. EOE. 494B

Cardiothoracic surgeon, board eligible or certified, recent training preferred. University practice, salaried position. Applicant must have experience with cardiac transplantation, pediatric cardiac surgery, and both pulmonary and esophageal surgery. Please send curriculum vitae.

Please respond to Box 495. 495B/C

Immediate opening for cardiothoracic surgeon for active practice of adult cardiac and general thoracic surgery in lovely seaside south Florida community. Must be mature, congenial, board-eligible individual with access to Florida license.

Please respond to Box 496. 496B/C

SITUATIONS WANTED

Cardiovascular and thoracic surgeon, 39, ABS, ABTS, excellent technique and results, personable. Seeks opportunity with new program or group practice.

Please respond to Box 468. 468A/D

Cardiothoracic and vascular surgeon, 44, ABS, ABTS wishes to relocate. Extensive experience in cardiac, thoracic, and vascular surgery. Would be interested in starting new program or association with established practice. Curriculum vitae and references upon request.

Please respond to Box 479. 479A/C

Cardiovascular and thoracic surgeon wishes to relocate. University trained, 38, hard working, experienced in all important aspects of adult cardiac, general thoracic, and vascular surgery.

Please respond to Box 484. 484B/C

General, vascular, and thoracic surgeon seeks first practice. Harvard-trained, ABS-eligible with extensive vascular experience and 1-year, noncardiac thoracic fellowship in England (just-completed).

Please respond to Box 485. 485B

FELLOWSHIPS

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819. 480A/F

Fellowship in pediatric cardiovascular surgery available July 1991. Experience includes surgery for hypoplastic left heart syndrome and arterial switch. A large, well-organized collection of heart specimens available for review. Illinois license or equivalent required. Salary and benefits in the high $40s.

Please respond to Division of Pediatric Cardiac Surgery, The Heart Institute for Children, Christ Hospital and Medical Center, 4440 W 95th St, Oak Lawn, IL 60453. 443L/C

Surgical residents/fellows—Clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart & Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, ext. 359. 445L/B

Fellowship in cardiovascular surgery: Fellowships for 1 to 2 years with busy service performing many complex cardiac procedures. 1989 cases—1,300. Opportunity to rotate in pediatric service. Foreign graduates must have ECFMG/FMGMS or be eligible for H-1 visa. US and Canadian graduates must be eligible for Oregon licensure.

Please send complete CV to Dr Albert Starr, 9155 SW Barnes Rd, Suite 240, Portland, OR 97225. 452L/B

A 2-year Cardiovascular Research Fellowship position is available 7/1/91 in the Division of Cardiothoracic Surgery at the University of Massachusetts Medical Center. This is an opportunity for a closely supervised and highly productive cardiac research experience. Requirements: (1) A minimum of 2 years of surgical training; (2) a commitment from an institution to complete the applicant's training in general surgery; (3) intentions to pursue an academic career in cardiothoracic surgery.

Interested candidates should contact Marc S. Visner, MD, Division of Cardiothoracic Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655; telephone: (508) 856-2975. 461L/E

Lung transplantation fellowship: The joint Montreal-Marseille Lung Transplant Program offers fully qualified surgeons an opportunity to spend 6 months each in Montreal and Marseille. Fellows will participate in donor and recipient selection, procurement, transplantation of single, double, and heart/lungs, and early and long-term care of recipients. The fellowship includes an opportunity to develop in-depth knowledge of the basic science of transplantation through intense courses given at McGill Center for Clinical Immunobiology and Transplantation. Hands-on experience in management of airway problems including bronchial laser and stent therapy under the supervision of Professeur J. F. Dumon will also be provided. An additional year of basic research experience is optional.

Please respond to Dr H. Shennib, Director, McGill Lung Transplant Program, Montreal General Hospital, 1650 Cedar Ave, Montreal, Que, Canada H3G 1A4. 470A/B

Cardiac surgical fellowship available at medical center doing a large volume of adult cardiac surgical procedures; program affiliated with the University of Miami, Florida. Medical license necessary, ideal for board eligible/certified general surgeon awaiting thoracic residency of board-eligible individual in thoracic surgery seeking additional experience.

Please respond with CV to Donald B. Williams, MD, Department of TCVS, Mount Sinai Medical Center, Miami Beach, FL 33140. 473A/C

Private practice fellowship in a very busy adult and pediatric cardiac surgical and transplant/artificial heart program. The fellowship terms can be negotiated. Must be in general or thoracic surgery training. Iowa license required.

Please respond to Box 486. 486B/C

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THE ANNALS OF THORACIC SURGERY

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*In clean-contaminated or potentially contaminated surgical procedures.

For a complete listing of indications and usage, please consult Brief Summary of Prescribing Information for ZINACEF on adjacent page.

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Zinacef*
(sterile cefuroxime sodium, Glaxo)

Zinacef*
(cefuroxime sodium injection)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zinacef* product labeling

INDICATIONS AND USAGE: Zinacef* is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing), *Streptococcus pyogenes*, and *Escherichia coli*
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* spp.
3. **Skin and Skin Stucture Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* spp, and *Enterobacter* spp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp
5. **Meningitis** caused by *S pneumoniae*, *H influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis* and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea**: Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females
7. **Bone and Joint Infections** caused by *S aureus* (including penicillinase- and non-penicillinase-producing strains)

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Zinacef has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Zinacef

Therapy may be started while awaiting the results of these studies, however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Zinacef may be used concomitantly with an aminoglycoside (see PRECAUTIONS) The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition

Prevention: The preoperative prophylactic administration of Zinacef may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (eg, vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Zinacef should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance

The perioperative use of Zinacef has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that Zinacef therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted

CONTRAINDICATIONS: Zinacef* is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

WARNINGS: BEFORE THERAPY WITH ZINACEF* IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered

PRECAUTIONS: Although Zinacef* rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function

The total daily dose of Zinacef should be reduced in patients with transient or persistent renal insufficiency (see DOSAGE AND ADMINISTRATION), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses

As with other antibiotics, prolonged use of Zinacef may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins

Drug/Laboratory Test Interactions: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest* tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape*). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Zinacef

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests

Reproductive studies revealed no impairment of fertility in animals

Pregnancy: ***Teratogenic Effects: Pregnancy Category B***: Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: Since Zinacef is excreted in human milk, caution should be exercised when Zinacef is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported

ADVERSE REACTIONS: Zinacef* is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS)

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with Zinacef and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown

In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics

Adverse Reactions: Toxic epidermal necrolysis, fever, vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated

Altered Laboratory Tests: Prolonged prothrombin time, pancytopenia, agranulocytosis, thrombocytopenia

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zinacef* product labeling.)

Impaired Renal Function: A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 1 in product package insert)

HOW SUPPLIED: Zinacef* in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Zinacef is a dry, white to off-white powder supplied in vials and infusion packs as follows

NDC 0173-0352-31	750-mg' Vial (Tray of 25)
NDC 0173-0354-35	1.5-g' Vial (Tray of 25)
NDC 0173-0353-32	750-mg' Infusion Pack (Tray of 10)
NDC 0173-0356-32	1.5-g' Infusion Pack (Tray of 10)
NDC 0173-0400-00	7.5-g' Pharmacy Bulk Package (Tray of 6)

Zinacef frozen as a premixed solution of cefuroxime sodium should not be stored above -20°C. Zinacef is supplied frozen in 50-ml, single-dose, plastic containers as follows:

NDC 0173-0424-00 750-mg' Plastic Container (Carton of 24)
NDC 0173-0425-00 1.5-g' Plastic Container (Carton of 24)

'Equivalent to cefuroxime.

October 1989
AB1 122

Glaxo Pharmaceuticals™
DIVISION OF GLAXO INC
Research Triangle Park, NC 27709

Zinacef* (sterile cefuroxime sodium): Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
Zinacef* (cefuroxime sodium injection): Manufactured for Glaxo Specialties Inc., Research Triangle Park, NC 27709 by Baxter Healthcare Corporation, Deerfield, IL 60015

ZIN450 Printed in USA February 1990

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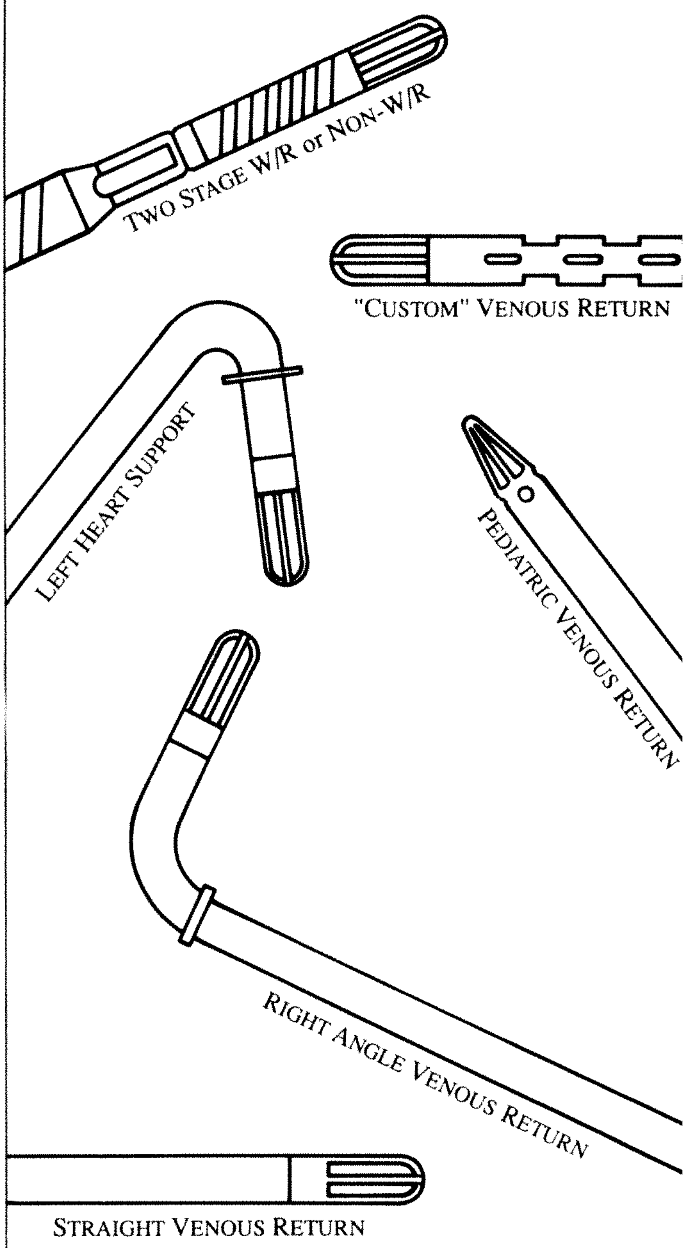

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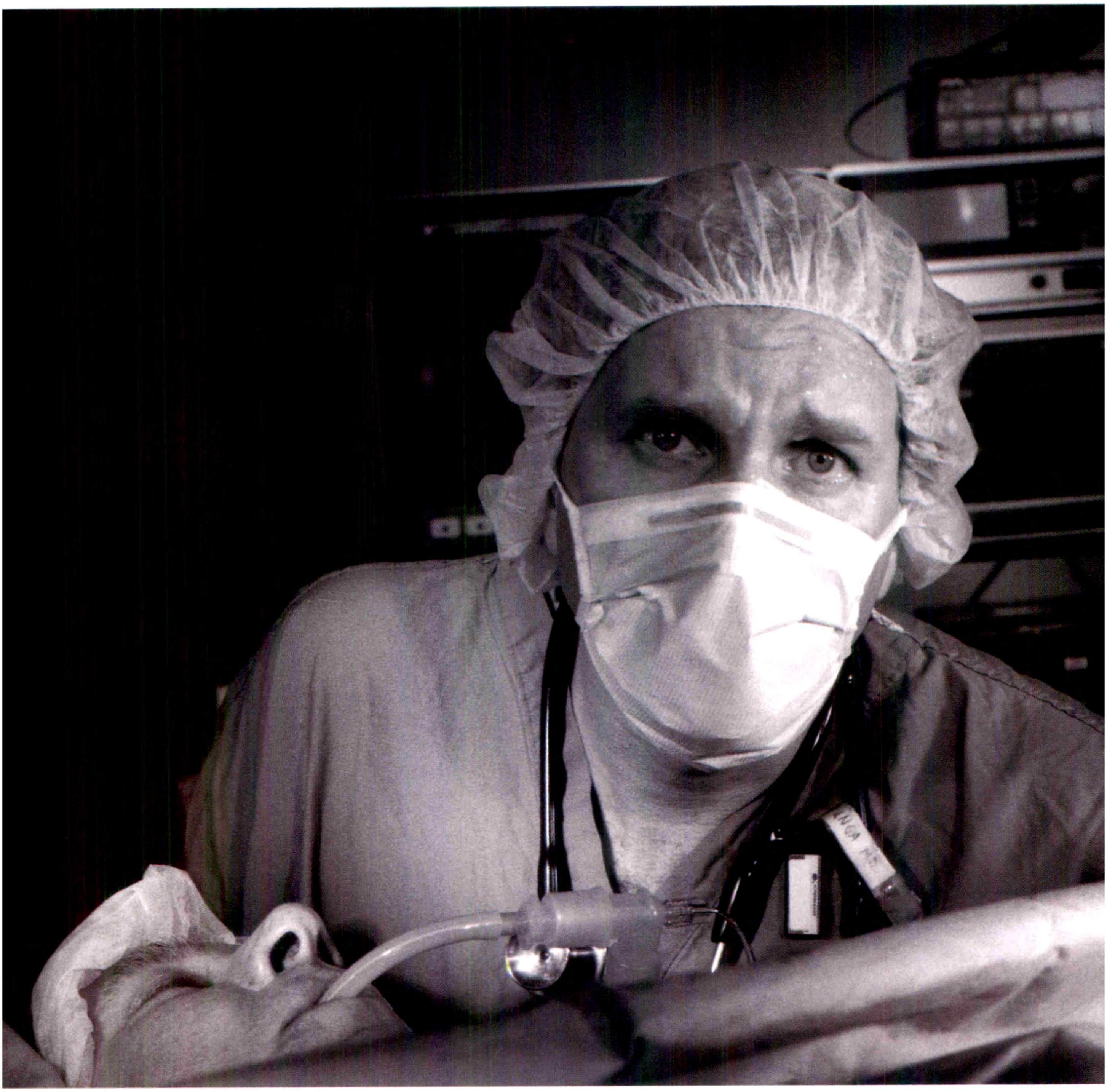

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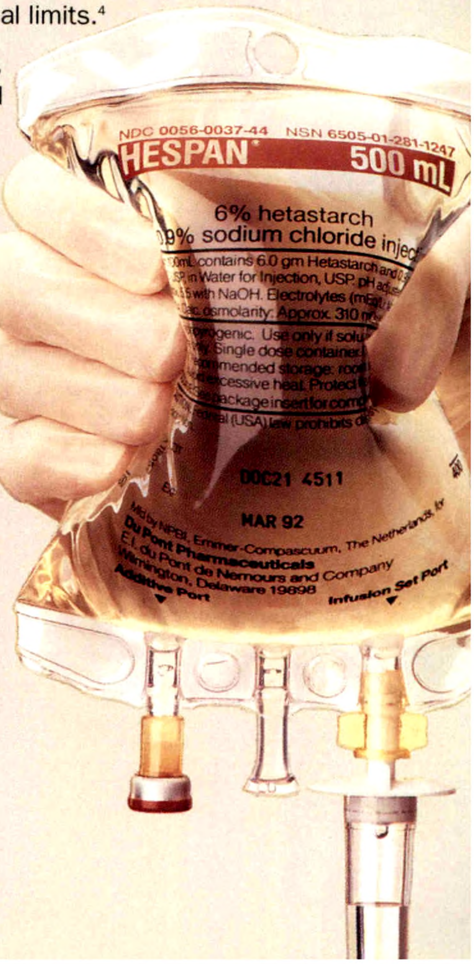
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References: 1. Moggio RA, Rha CC, Somberg ED, Praeger PI, Pooley RW, Reed GE. Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med.* 1983;11:943-945. **2.** Kirklin JK, Leil WA, Kouchoukos NT. Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg.* 1984;37:40-46. **3.** Diehl JT, Lester JL, Cosgrove DM. Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg.* 1982;34:674-679. **4.** Gold MS, Russo J, Tissot M, Weinhouse G, Riles T. Comparison of hetastarch to albumin for perioperative bleeding in patients undergoing abdominal aortic aneurysm surgery: A prospective, randomized study. *Ann Surg* 1990;211:482-485.

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WARNINGS

Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of HESPAN. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count, hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/mL (normal 0.0–7.0 mg/mL) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS

The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing) bleeding due to hemodilution (see Warnings), and circulatory overload and pulmonary edema (see Precautions).

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion: HESPAN is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred

Dosage in Leukapheresis

250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The safety and compatibility of other additives have not been established.

HOW SUPPLIED

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

HESPAN is supplied sterile and nonpyrogenic in 500 mL intravenous plastic infusion containers (NDC 0056-0037-44) and 500 mL intravenous glass bottles (NDC 0056-0037-05).

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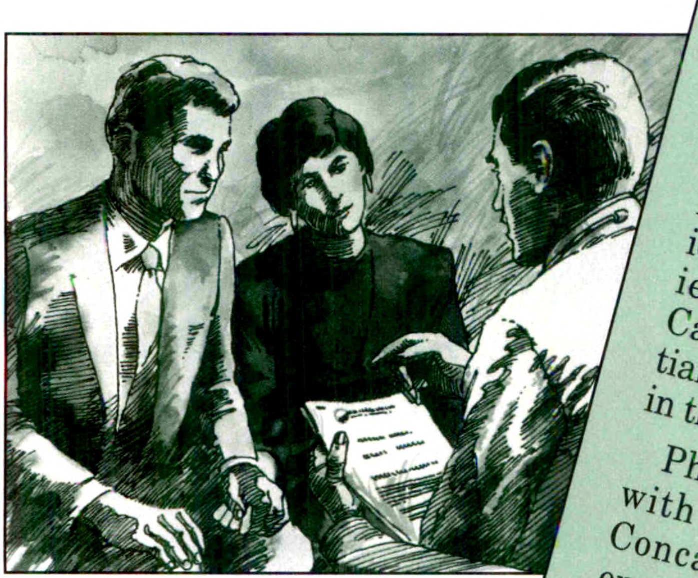

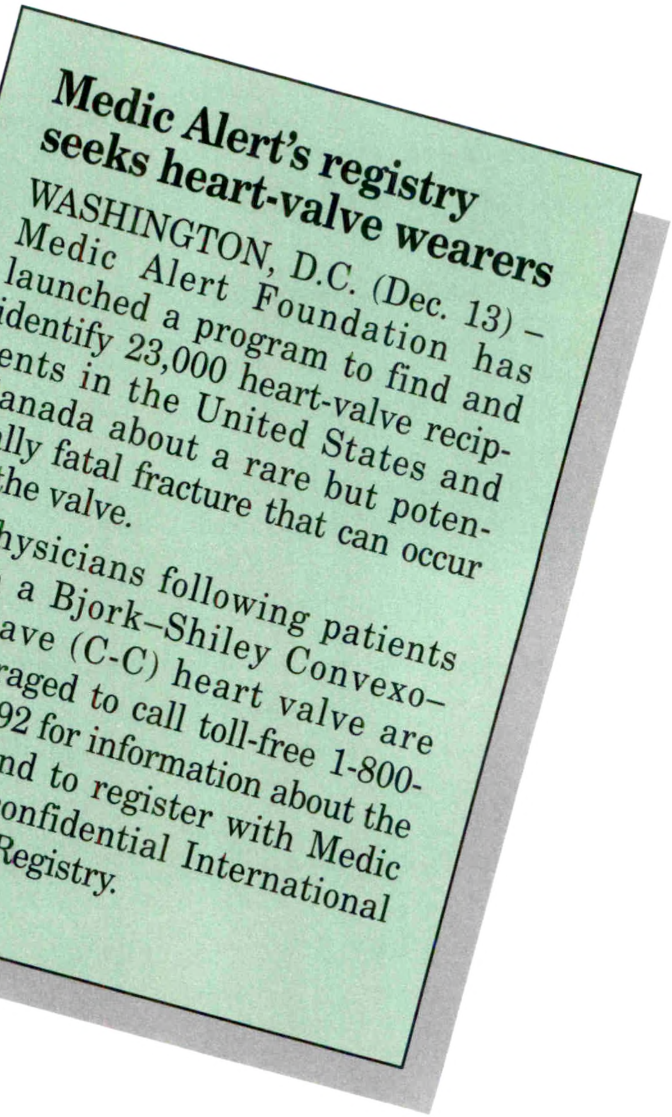

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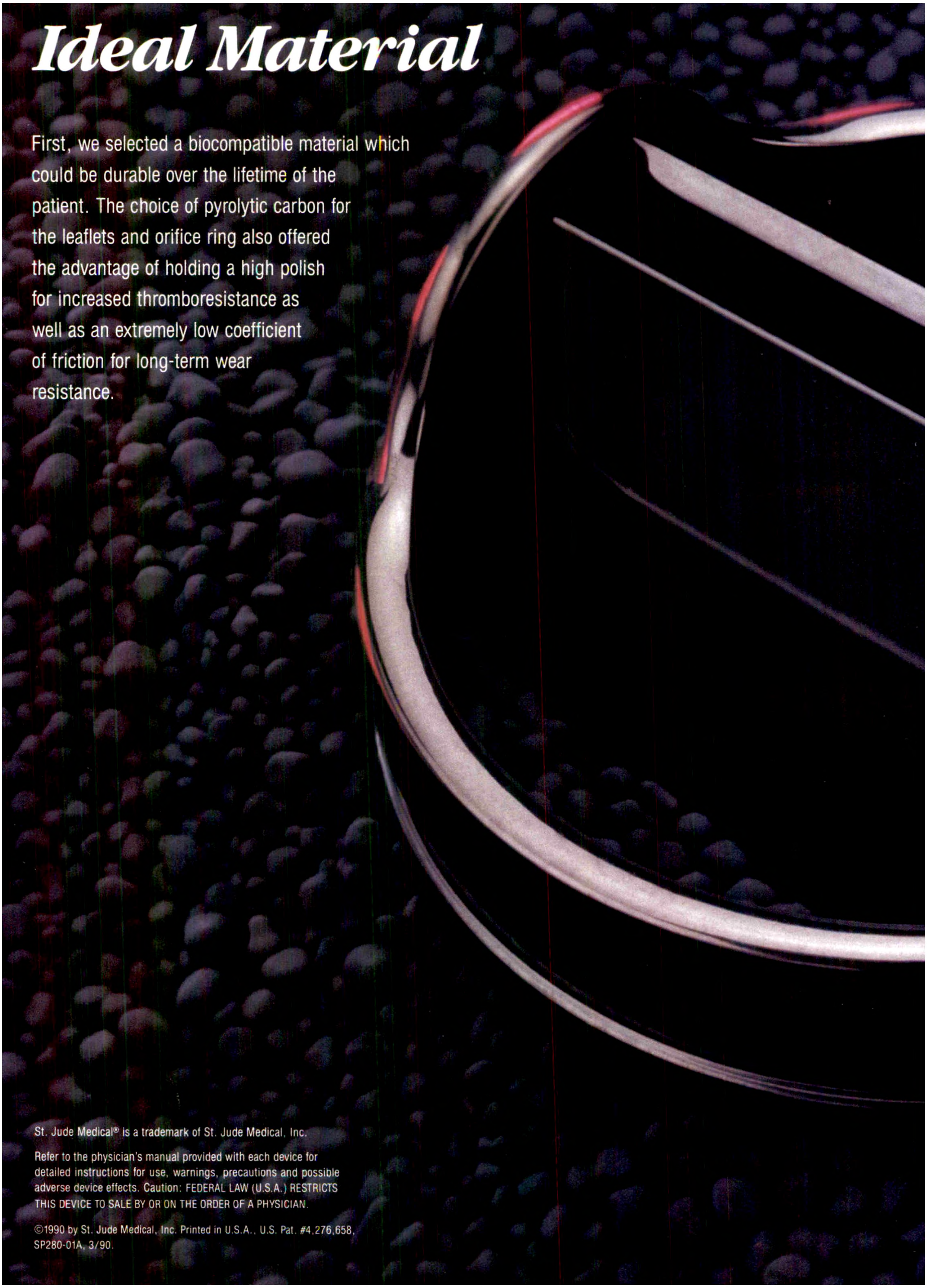

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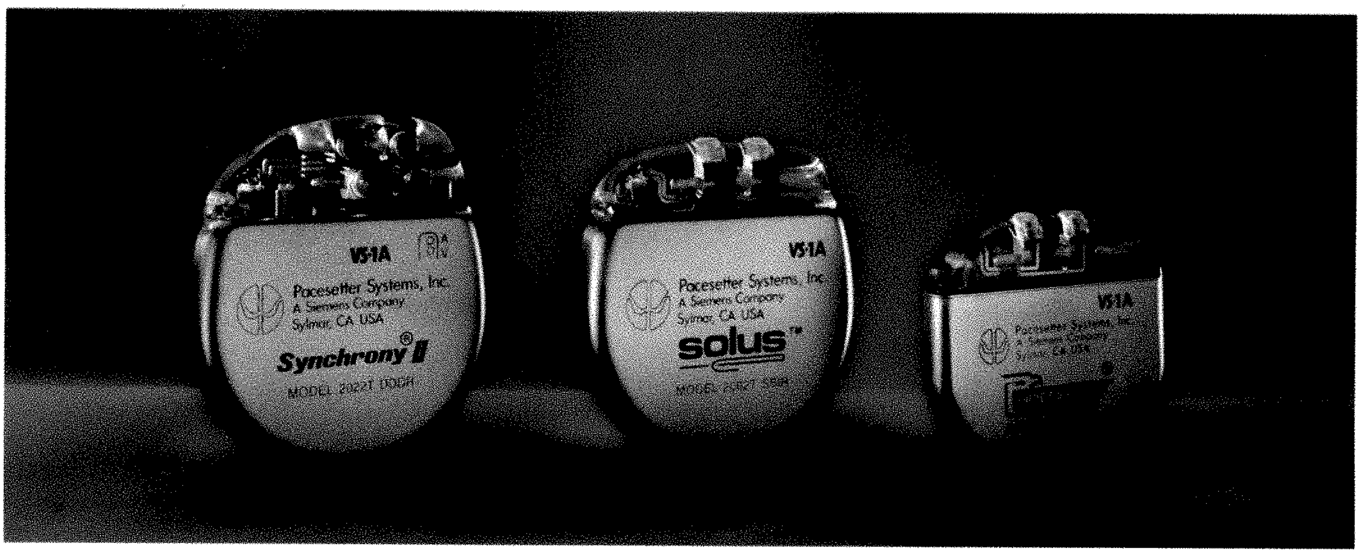

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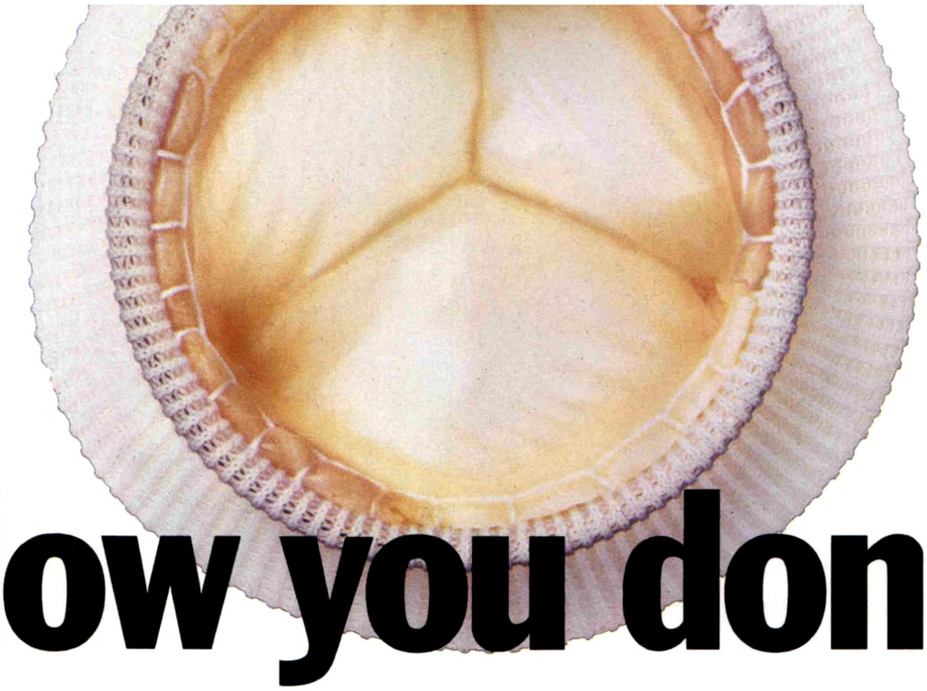

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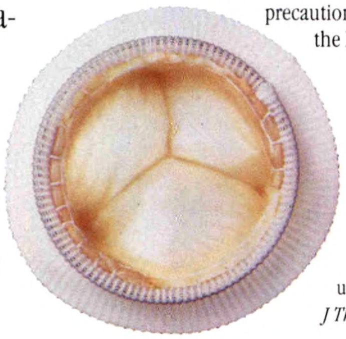

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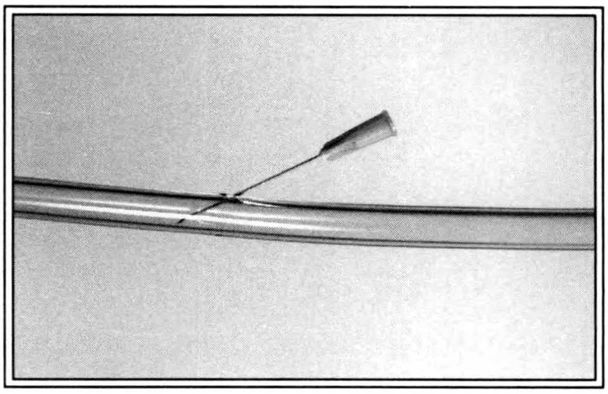

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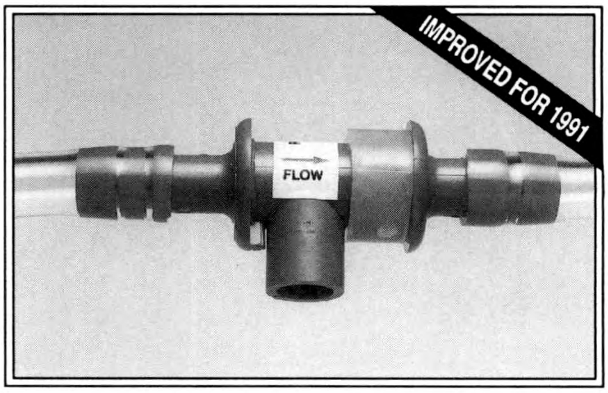

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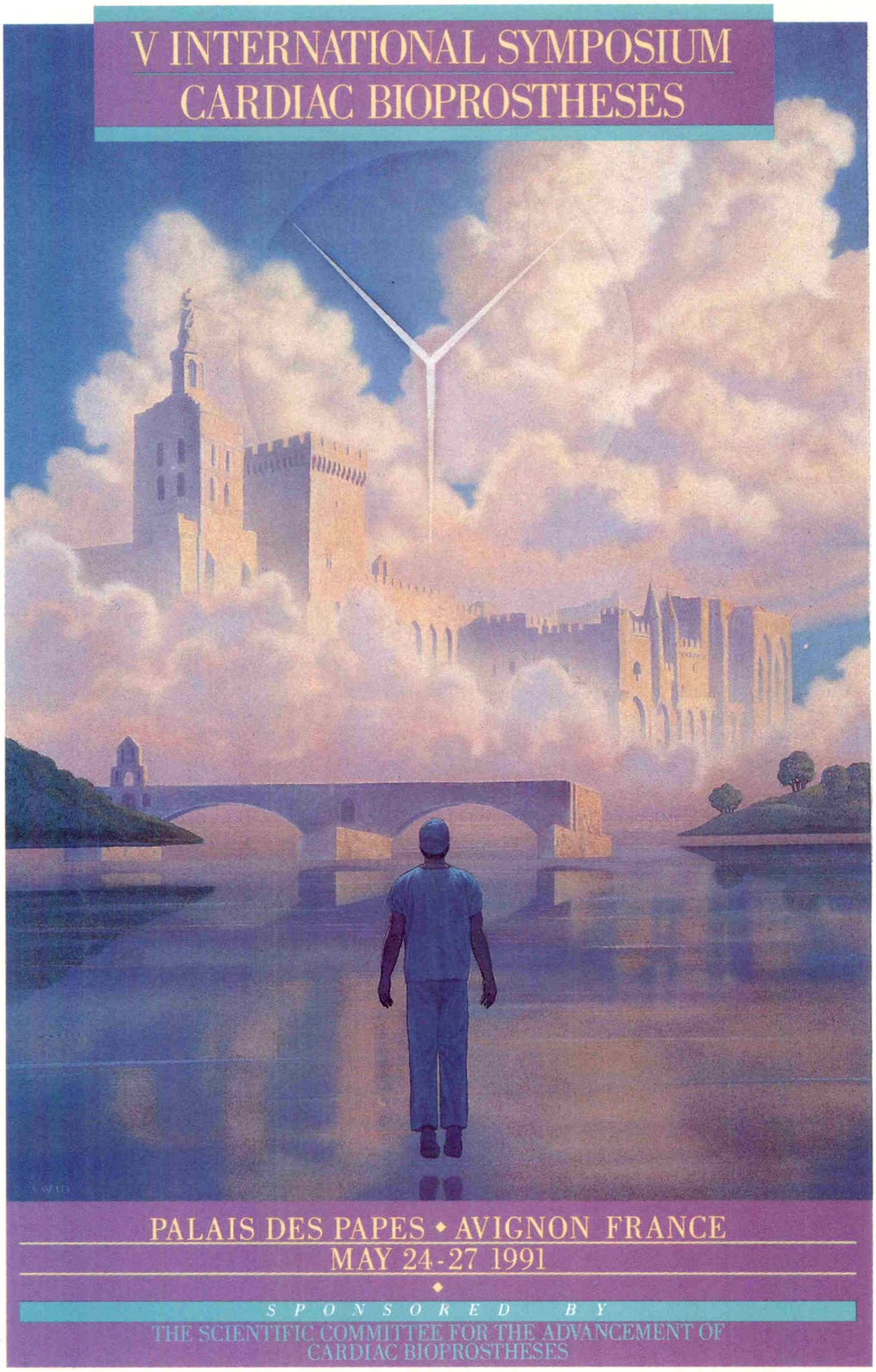

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Preparation, Trust, and Responsibility

Harvey W. Bender, Jr, MD

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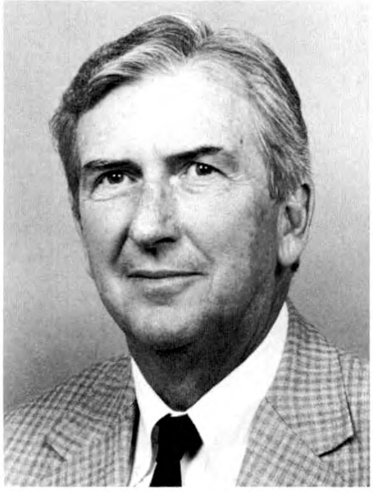

It is a singular honor for me to be selected to preside at this, the Thirty-seventh Annual Meeting of the Southern Thoracic Surgical Association (STSA). During my membership in this Association, I have seen the STSA grow from a small nucleus of thoracic surgeons with similar interests to a multifaceted organization containing within its membership individuals with expertise and international recognition in all aspects of thoracic surgery. The annual scientific programs of the STSA are consistently well balanced, covering important contributions throughout our specialty. The growth and direction of the postgraduate course have been exemplary as evidenced by this year's program.

I am extremely grateful to the membership for electing me to this office, recognizing that you do me honor and, at the same time, provide me with the opportunity to speak to a captive audience. I am also counting on the fact that most of you in this room today grew up in Southern households, so that it would not be unreasonable for me to expect your criticism to be kind.

Presidential addresses tend to fall into one of three categories. The first is for the president to present a scientific paper based on an area of his or her special interest and one that frequently chronicals important advances in the management of a disease process. The second general type of presidential address is historical, one that reviews and documents important turning points in the development of the specialty and emphasizes the important roles played by previous leaders in the field. The third type is frequently referred to as philosophical and, although I am not much of a philosopher, there are things that I feel need to be said about our specialty and about the way that we will move into the twenty-first century.

As we all know, much of the direction in our lives depends on opportunities that occur at various times and places. It has been my good fortune in the last several years to have the opportunity to be involved in postgraduate education in our specialty at a national level. During that time, I served as a member of the Thoracic Surgery Residency Review Committee, the Surgery Residency Review Committee, the American Board of Thoracic Surgery, and the American Board of Surgery. The Residency Review Committees consist of representatives from the American College of Surgeons, the American Medical Association, and the related specialty Board. This committee then has the responsibility of reviewing and accrediting residency programs. The Boards, as you know, are responsible for establishing the criteria for admission and for the conduction of the certifying examination. These jobs have given me the opportunity to devote a great deal of thought to the methods we currently use to prepare individuals for the practice of thoracic surgery in the future and an opportunity to look at both good and bad aspects of that preparation.

The title of the talk today is "Preparation, Trust, and Responsibility." These represent three important aspects of the field of thoracic surgery and of thoracic surgeons. I will attempt to address each of these issues in varying detail. I would like to preface my remarks by stating that what I say today represents my own personal thoughts and in no way represents the position of the American Board of Thoracic Surgery or the Thoracic Surgery Residency Review Committee.

Obviously it is our desire to prepare individuals to practice the specialty in a manner that is safe, effective, and accomplished without forgetting the human needs of our patients. It goes without saying that during the course of the residency, we must teach the principles of pathology and physiology as they relate to thoracic disease. We must provide an environment conducive to the acquisition of the knowledge and manual skills necessary to perform today's operative procedures. We must also provide a faculty with clinical expertise in the spectrum of thoracic surgery today and inquisitive and innovative enough to participate in future advances, this being done in a way that provides a base to which the changes necessary to stay current in the future practice of thoracic surgery can be added. And finally, I feel it is extremely

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Presented at the Thirty-seventh Annual Meeting of the Southern Thoracic Surgical Association, Dorado, Puerto Rico, Nov 8–10, 1990.

Address reprint requests to Dr Bender, Department of Cardiac and Thoracic Surgery, Vanderbilt University Medical Center, 2986 The Vanderbilt Clinic, 1301 22nd Ave South, Nashville, TN 37232-5734.

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Fig 1. Dr Michael E. DeBakey.

important that we instill the commitment to the management of all aspects of the patients' illness and not restrict our teaching to operative surgery. It is not hard to come up with these objectives, and I think few in the audience would argue with their importance. The way we accomplish this, however, is different among many of our training programs today and certainly has varied a great deal over the past two decades as we look back at thoracic surgical training and the changes that have occurred.

As I began to think about what I should talk about on this occasion, I reflected on the events in my own training that seemed to be effective. Role models are obviously very important in our education at all levels. We are all influenced by many individuals and by many events that lead us on whatever path we eventually take in our careers. I had the good fortune to come in contact with two very strong departmental chairmen who worked in the field of cardiac and thoracic surgery during my time in medical school and residency training. Their influence is felt almost daily in my practice. As a medical student I had the opportunity to have close contact with Dr Michael DeBakey (Fig 1) at a time when the advances being made in the fields of cardiac and vascular surgery at the Baylor University School of Medicine were at an accelerated pace and where the atmosphere was truly one of excitement and great optimism for the future. The contributions made by Dr DeBakey during his career are phenomenal. His contributions are recognized in almost all areas of surgery, and at the same time his role in the development of Baylor Medical College is too large to measure.

After graduation from medical school, I happened to be selected for a surgical internship and subsequent residency at the Johns Hopkins Hospital. There, under the influence of Dr Alfred Blalock (Fig 2), the program emphasized the importance of a broad education based on sound principles of pathology and physiology as well as the fundamental principles of surgery. The fact that surgical principles were taught and emphasized as opposed to teaching specific operative procedures must have helped Dr Blalock's residents as they went on to play important leadership roles in surgery over an extended period of time. As I look back on that period of training, I have frequently tried to analyze and determine the features that allowed Dr Blalock's program to be so successful. First, the program was small, yet filled with individuals of high caliber. Because the program was small and under one roof, there was constant contact between the junior residents and the senior house officers and faculty, with easy, open discussion regarding clinical medicine and research. The schedule of rotations was well thought out and designed to provide increasing responsibility as the principles of surgery were applied. But equally important were two essential features that were a part of every surgical service in the hospital at that time. First, the programs were all primarily devoted to patient care with each individual patient assuming a primary position. In contrast to today where the monitoring of the quality of care is directed toward establishing tight paper trails, usually generated by large numbers of hospital staff at great expense, the monitoring of patient care at that time was much more direct and much more personal. If you did not do the work well you did not get much work to do and you were not kept on for the next year. The patient was clearly the most important aspect of the program and any result that was less than desirable prompted a great deal of scrutiny. Finally, a thread that was woven through the fabric of the program was the fact that the individual surgeon, whether that surgeon was a resident or an attending, bore total responsibility for any result that was less than optimal. That responsibility included every aspect of the patient's care from admission to final disposition. The ability to take a hard, honest look at each of our results as we practice our speciality is extremely important and one that will always stand us in good stead. Although this is easier said than done, it usually results in a more positive physician-patient relationship than medicine as a whole has recently enjoyed.

Of interest in view of today's topic is that the training program in thoracic surgery at the Hopkins Hospital at that time was nonapproved. Its nonapproval was not unique in that there were a number of other very important thoracic surgical training programs in this country 25 years ago that did not have the approval of the Residency Review Committee or the Board of Thoracic Surgery.

Fig 2. Dr Alfred Blalock.

Could it be that the fact that these programs did not have clearly defined rotations to meet the requirements of the Residency Review Committee was actually important in allowing them to assume leadership roles?

The importance of Certifying Boards and Residency Review Committees is well known to all of us, and that will not be argued today. On the other hand, one real risk of setting requirements and insisting that all programs meet each of the requirements is the risk of having all programs begin to look alike with a tendency to move toward mediocrity. If our specialty is going to move into the next century and be on the leading edge of the changes in medicine in the future, we must prepare individuals who will be equipped with a base of knowledge that will be broad and comprehensive enough to allow them to build on that base as changes are necessary and to participate in the exciting new developments that are sure to come.

I think that the great majority of individuals in this audience who are practicing cardiac surgery will agree that the operative procedures that they perform today are, in large part, operative procedures that have been developed since they completed their formal training. This certainly holds true for those doing general thoracic surgery in that a knowledge of chemotherapy, radiation therapy, and in the future perhaps gene manipulation will be extremely important in the management of patients with malignant disease. The problems encountered by thoracic surgeons involved in caring for patients with the pulmonary complications of immunosuppression, whether viral or chemotherapeutic in origin, were not anticipated during the training of most of us. Yet it appears that we will see those patients with increasing frequency in the future. In spite of these changes, the basic requirements for training in thoracic surgery have changed little since the development of the first thoracic surgical residency at the University of Michigan in 1928. At that time, it was recognized that there needed to be 2 years dedicated to thoracic surgical training after completion of general surgical training. Now, 62 years later, the requirements of the American Board of Thoracic Surgery are still 2 years of dedicated thoracic surgical training after completion of a residency in general surgery and certification by the American Board of Surgery. The changes that have occurred in our specialty during that 62 years have been enormous. The field of pulmonary surgery is no longer the surgical treatment of inflammatory disease, where the most frequent operative procedures were the drainage of empyema and thoracoplasty. Today's pulmonary surgeon not only needs to understand the treatment of inflammatory disease but also must be knowledgeable in the management of primary and metastatic neoplasms in the chest, obstructive airway disease, the pulmonary complications of immunosuppression, and transplantation. The changes in endoscopy alone have resulted in some of us limiting our practice to that area. The entire field of cardiac surgery has developed in the interim, with the treatment of the most complex forms of congenital cardiac malformations, myocardial revascularization, transplantation of the heart and lungs, and precise reparative surgery of deformed valves frequently performed. Also, in recent years a whole new field of cardiac surgery has been added, the treatment of patients with both atrial and ventricular arrhythmias.

Many of the program directors of thoracic surgical training programs have recognized the need for additional training and have designed programs that attempt to meet that need. In many instances, these program directors have met resistance on the part of the Board and the Residency Review Committee because the programs did not meet the cut and dried criteria that had been established. It has been felt by some that attempts to increase the length of thoracic surgical residencies was a veiled attempt to allow trainees to get the required number of cases in 3 years as opposed to 2 years. This resulted in the American Board of Thoracic Surgery sending a message to the Residency Review Committee that if programs were to lengthen to 3 years, the same intensity of operative experience must be maintained throughout each of the 3 years. In fact, what is probably needed is not another year in the operating room for the resident, but a year in which he or she may prepare by gaining in-depth knowledge in the basic sciences and related fields that apply to our specialty. I think that all of us would agree that lengthening the time of training is, in itself, not an answer to preparation for the future. Instead I think we have an obligation to look carefully at the training we are now providing and ask ourselves if that is the best training to allow us to move with the advances that are sure to come in medicine.

In the past 20 years there has been considerable change in the experience of candidates who apply for examination by the American Board of Thoracic Surgery. There has been a steady increase in the number of operations performed with some change in the types of procedures carried out. From my experience with the oral examinations of the American Board of Thoracic Surgery, there is also clear evidence of steadily declining involvement of the resident in patient management outside the technical manipulations of the operative procedure. Some of the responsibility for this must be borne by the American Board of Thoracic Surgery, as programs came under pressure to ensure that their candidates were not below the thirtieth percentile in operative experience because those individuals were singled out and referred to the Credentials Committee for closer scrutiny.

Illustrated are a comparison of the operative experience of thoracic surgical residents as primary surgeon during 2-year thoracic surgical training programs (Fig 3). The years selected are 1971, because that was the earliest period in which we have the data in this form, 1989, because that is the most recent year from which we have these data, and 1980 as a midpoint during that period. All numbers represent mean figures among candidates accepted for examination. Figure 3A shows the experience with pulmonary resections and esophageal procedures in those three time periods. The increase here has not been great and possibly represents a shift from assistant to surgeon and not an actual increase in material. One worrisome feature on many applications reviewed by the

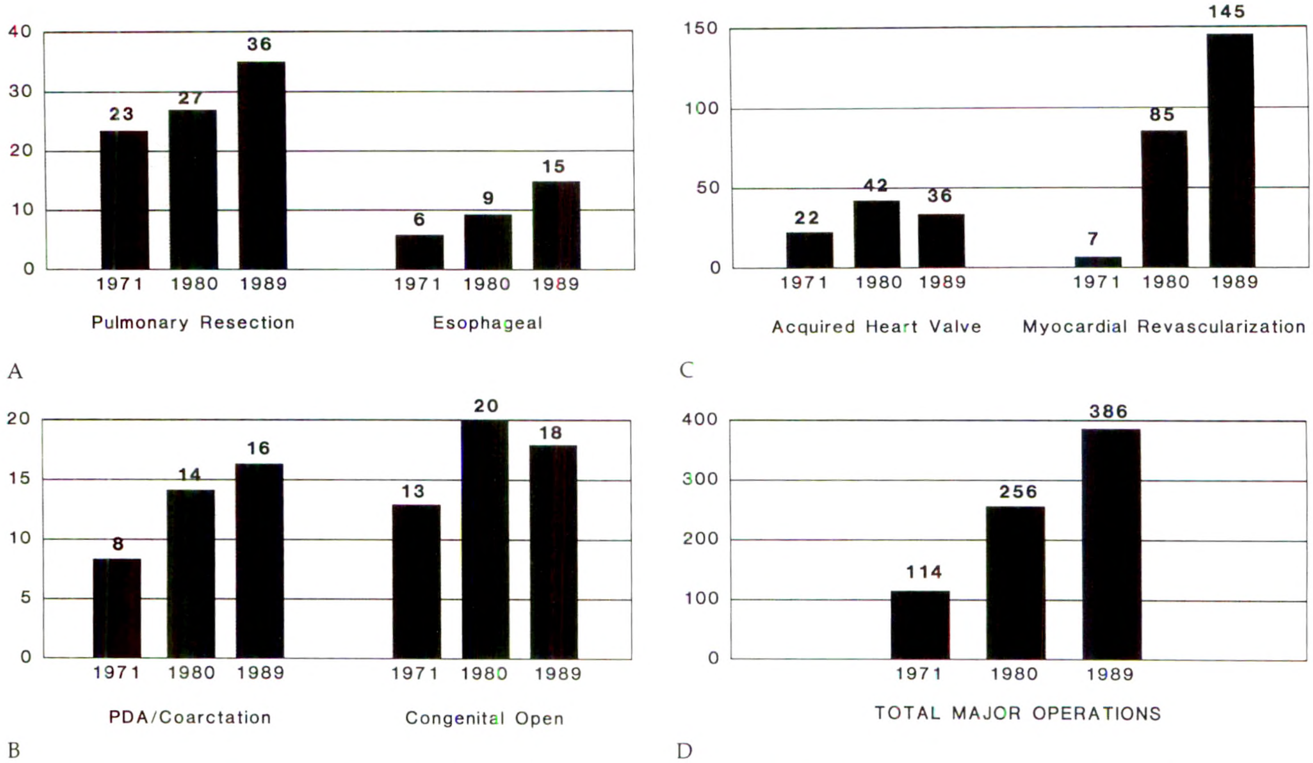

Fig 3. Operative experience of thoracic surgical residents as primary surgeon during 2-year thoracic surgical training programs. (PDA = patent ductus arteriosus.)

Residency Review Committee is that most if not all of the pulmonary and esophageal case material is listed with the resident as the primary surgeon. When this occurs it is reasonable to question the expertise of the faculty after a period of time, as I believe that the occasional surgeon is unlikely to be an innovative and effective teacher.

Figure 3B illustrates the experience in the category of patent ductus arteriosus or coarctation (or both) and open congenital cardiac procedures. It is of interest that the number of open procedures has decreased in the last decade, which would appear to be due to the fact that so much of children's intracardiac surgery today is directed to the repair of complex malformations in the neonatal period. These operations are frequently performed by the teaching staff.

Figure 3C shows the numbers for acquired (or valvar) heart disease and myocardial revascularization. There is obviously a great increase in the number of operations for myocardial revascularization. At first glance this increase seems unnecessarily high, but we must remember that this operation will clearly be the mainstay of most cardiac surgical practices in the forseeable future. Still, one must question the number of these operations necessary to learn to perform them safely and effectively, particularly if the trainee had been taught sound surgical principles and had developed the manual dexterity required to use the instruments well.

The last of this group of illustrations (Fig 3D) shows the increase in total operative procedures as primary surgeon during these two decades. You can see that the mean went from 114 in 1971 to 256 in 1980 and 386 in 1989. Remembering that the length of the residency in each of the time periods was 2 years and that this does not include first assistant cases, this represents a substantial increase in the amount of time during the residency spent in the operating room. You should also remember that the American Board of Thoracic Surgery lists 180 as the minimal number of cases, as primary surgeon during the residency, necessary to sit for the examination. For the sake of discussion let us assume that each of these operative procedures is one half of an operating day. The difference between the number of operations in 1989 and 1971 is 271 procedures. If each procedure represents a half-day's operating room work, that is 135 operating days or 4½ months that have been changed from nonoperating to operating time during the residency. This, of course, does not take into account the increase in time spent as first assistant. I am less concerned about the increase in time spent in the operating room than I am about the decrease in time spent outside the operating room. That is time that could be spent in the library, the cardiac catheterization laboratory, the endoscopy laboratory, or at the bedside. I am afraid that we are clearly sending a message to our trainees that thoracic surgery is an operating room specialty.

The attitude that thoracic surgery is an operating room specialty must clearly have played a role in the fact that much of what was once a part of the specialty of thoracic surgery is now in the hands of other physicians. Needle biopsy of intrathoracic tumors now clearly falls into the hands of the radiologist, bronchoscopy has become a part of the pulmonary medicine physician's domain, and in many institutions our cardiac surgeons no longer put in cardiac pacemakers. Of more concern, however, is that in many institutions the postoperative management of cardiac and thoracic surgical patients is under the direction of an intensive care specialist. We are unlikely to regain that which has been lost from our specialty; however, to be moved out of the intensive care unit is to abandon the soul of our specialty. We must instill in our trainees the fact that the care of thoracic surgical patients includes all aspects of their preoperative and postoperative management. To accomplish this we must provide time for our residents to be involved in more than the operative care of thoracic patients. And if we are going to function as role models, we must see that we as practitioners and faculty are also involved outside the walls of the operating room.

From the preceding data there appears to be no lack of operative experience for a thoracic surgical trainee, so let us look for a minute at the training in general surgery before beginning a thoracic surgical residency. General surgical training that was available to the older members of this association was clearly different from general surgical training that is now available to our residents in at least five ways:

1. Loss of resident service
2. Loss of pyramidal structure
3. Increase in size of programs
4. More "high tech"
5. Most graduates take additional training

The social changes that resulted in the loss of large populations of ward patients has clearly altered the ability to allow for the graded responsibility and maturation that was an important part of general surgical training in the past. These social changes were appropriate and it is up to us to be able to train surgeons in the environment of today. In the past, general surgical residencies were pyramidal and very competitive, with those residents considered to be the most capable advancing. Then it was clearly advantageous for the American Board of Thoracic Surgery to take advantage of general surgical selectivity and made good sense to require prior certification by the American Board of Surgery. Today if a medical student decides that he or she wants to complete general surgical training and matches for a surgical residency, the individual is almost certainly assured of finishing as chief resident. As residency programs have grown in size, multiple hospitals are involved with shorter rotations and a relationship with the faculty that is more distant. In addition, many changes have occurred on general surgical services with improvements in technology so that fewer knots are tied, more hemoclips are applied, few bowel anastomoses are made freehand, and increasing numbers are made with a surgical stapling device. I will make no value judgment on the precision of these anastomoses or their incidence of complications. I will only say that making a stapled anastomosis does little to prepare the surgeon for the fine suturing that will be necessary in intracardiac operations in infants. To me the rotation of a well-designed flap to cover a decubitus ulcer would be better preparation. In that operation there is a need to visualize the defect, design the flap, rotate it into position, and meticulously sew it in place so as not to embarrass the blood supply. At the present time, the majority of individuals completing general surgical training go on to additional training in one or more of the surgical specialties, so that there is no longer as much pressure on the general surgical program director to be assured that the individual completing the chief residency is a mature surgeon ready to take on the responsibilities of a surgical practice. The requirements that are placed on program directors in general surgery are such that the residents must rotate through many services that are felt to be a part of the general surgical world, and, in many instances, these rotations are necessary to prevent further fragmentation of general surgery. It may well be that part of the 5 years required for general surgical training before entering a thoracic surgical residency could be better spent if we designed a curriculum that was truly directed toward preparing the individual for clinical training in thoracic surgery, or perhaps we could shorten general surgical training and lengthen thoracic surgery training without necessarily increasing the number of thoracic surgical operations performed.

In the early 1970s there was a movement to establish thoracic surgical training programs as separate entities with the establishment of the requirement that residents from nonapproved programs would no longer be eligible for examination by the American Board of Thoracic Surgery. Although that sounds desirable, one side effect was the fact that thoracic surgical training program directors became more removed from the activities of the general surgical services. We then began to look at general and thoracic surgical training as two disconnected units, totally separated. This has now been developed to the point where there is a separate match for thoracic surgical residencies. Instead of trying to coordinate the goals of training in thoracic surgery and in general surgery, we have been more concerned with our independence.

At the present time, program review by the Residency Review Committee for Thoracic Surgery and candidate review by the American Board of Thoracic Surgery place a great deal of emphasis on numbers of cases available to the program or to the specific candidate. This has obviously resulted in a steady inflationary spiral in numbers of procedures in an attempt to be sure that each program and each candidate meets the respective requirements.

It would seem to me that during the period of general surgical training there is clearly an opportunity to develop a curriculum that would provide very good preparation for an individual going on to a specialty in thoracic surgery, one that would give each individual a sound base in pathology, surgical technique, and the management of the critically ill patient. If this could be done in 4 years as opposed to 5 years and still be acceptable to both Boards, it would clearly free up additional time for training in the specialty of thoracic surgery that could be more comprehensive in scope. This certainly seems feasible now that it is generally accepted that the fourth (or senior) year of

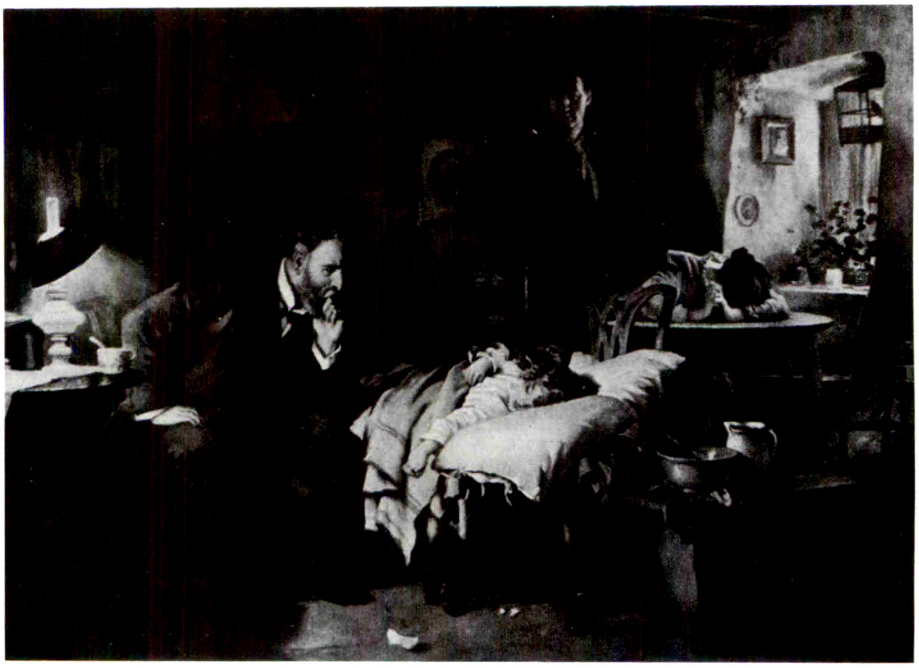

Fig 4. "The Doctor" by Sir Samuel Luke Fildes, 1891 (The Tate Gallery, London).

general surgical training is essentially the same as the chief resident year. If this were to be accomplished, the role of the program director in both general surgery and thoracic surgery becomes very important. This is where the importance of "Trust and Responsibility" comes into the discussion. If a truly coordinated effort is made to create a training program in general and thoracic surgery, it will have to begin at the selection and recruitment of entry-level house officers on the surgical service. This will mean that thoracic surgical faculty members will have to be very involved in the selection of first-year residents and that the program directors in thoracic surgery and general surgery will have to cooperate in designing a curriculum during the general surgical training. That training must serve as a surgical foundation to which thoracic surgical training can be added, and, at the same time, qualify the candidate for examination by the American Board of Surgery.

To provide for adequate training outside the operating room, it is essential that we allow more flexibility in programs and that we trust the program director to provide an adequate curriculum to accomplish the desired training. At the same time, program directors must earn that trust and assume the responsibility for that training. They must direct their attention specifically to the training aspects of their program so that all aspects of training can be addressed. This will mean that a great deal of the service needs of our programs will have to be met by individuals outside the resident staff. This may result in the need for increased faculty, as well as the increased use of surgical assistants and clinical nurse specialists to allow for the smooth functioning of the service on a continuing basis. The easy way out is to keep the resident in the operating room where he or she provides very good assistance and to staff the intensive care units with personnel who are there on a long-term basis and not rotating through as our house officers do. That is a very short-sighted approach and one that, although it may make our lives easier for the present, will do nothing toward maintaining a continuing supply of well-trained thoracic surgeons for future generations.

Before I close, I would like to show one slide (Fig 4), that of the painting by Sir Samuel Luke Fildes entitled "The Doctor." We have talked some this morning about trust and responsibility as related to program directors and accrediting and examining Boards. The greatest trust that we deal with is experienced on a daily basis as family members trust us to perform complex operative procedures on their loved ones. Today when we are constantly dealing with HMOs, PPOs, IPAs, and various third party agencies, there is a tendency to begin to think in terms of physicians being health care providers and patients as being customers. And yet if you look into the tear-filled eyes of the parents of a small baby or witness the kiss of an elderly couple as the patient is being wheeled to the operating room, it is clear that those individuals view this as a very personal experience. They have entrusted us with that which is their most precious possession and hope for the future, and it is the way that we as individual physicians handle this responsibility that will determine the level of medical care that is practiced in the future. I thank you for this opportunity and your attention.

Valve Re-replacement in the Asymptomatic Patient

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Bortolotti and associates [1] from Padova, who report in this issue on the Hancock pericardial valve, have had long and extensive experience with biological valve cardiac replacements. As many will recall, they were one of the original six units (Oklahoma City, Brigham and Women's Hospital, Stanford, Henry Ford, and the National Institutes of Health) that implanted Hancock porcine bioprosthetic valves beginning approximately 1970. With their long experience, they know the technical details of bioprosthetic valve implantation and have helped to "write the book" on biological valve durability. They have made us keenly aware of the necessity of careful observation of patients with biological valves, particularly in the younger age groups that are commonly operated on in western Europe.

This experienced group now reports their experience with the Hancock pericardial graft, a short-lived commercial attempt to compete with other pericardial heart valves. At the time of development of this valve, the Ionescu-Shiley pericardial valve had received large worldwide attention, especially in the United States. The stated main advantage of pericardial valves over porcine valves was hemodynamic, providing a better effective orifice area at any given annular diameter, a fact generally borne out though not as significantly as once thought. The early and late results are of interest in this series. Patient survival, both early and late, is rather poor after replacement with this valve, perhaps reflecting a selected group of very ill patients. Of the relatively small numbers of patients, a large percentage of operative survivors over a relatively short follow-up period (approximately 5 years), had valve dysfunction necessitating reoperation. There was also a disturbing number of episodes of endocarditis for which reoperation was also necessary. Thirty-four of 76 patients (45%) at risk required reoperation during the follow-up period, an unacceptable rate. Unlike other series of biological valve replacements, there was a higher rate of reoperation in patients with aortic valve replacement than in those with mitral valve replacement. These data conclusively document unacceptable problems with this particular valve, and we conclude it was an ill-fated attempt to attain a market share in the general area of pericardial valves in the late 1970s and early 1980s. Fortunately, this valve was not widely used, as the users were alert to early problems and reported them promptly, causing the company to withdraw the valve and alerting other surgeons.

See also page 430.

What about the few patients who may have this valve in place, who may be doing well, clinically similar to patients with the Braunwald-Cutter valves in the 1980s and those with the convexo-concave Björk-Shiley valve of the late 1980s and early 1990s, other recent valve recalls? Is prophylactic valve reoperation indicated in asymptomatic patients? The risk of reoperation in large centers that do this often is clearly related to the functional class of the patient at the time of operation. In our own experience, patients who are in functional class III or less have no greater risk for reoperation than a patient undergoing a primary valve replacement, whether it be aortic, mitral, or multiple valve. However, when the patient is seriously decompensated and in functional class IV, the operative mortality rate increases about threefold. So clearly, the timing of operation for valve re-replacement is a paramount consideration.

There is increasing evidence that the "natural history" of pericardial valves is different than that of the porcine valve, and such valves appear to be considerably shorter-lived. Should asymptomatic patients with any pericardial valve undergo reoperation? Bortolotti and associates make a cogent case for this approach. If anyone in the world now has a Hancock pericardial valve left in, such a valve should be removed on an elective basis by surgical teams that do reoperations often and do them well. The worst circumstance is to offer an asymptomatic patient reoperation by a surgical team that does not do reoperations very often, therefore exposing that patient to an increased operative risk. Obviously, any patient that has the appearance of a new murmur, regardless of symptomatology, should undergo "prophylactic" elective valve re-replacement. Patients who have the appearance of a new murmur and symptoms should undergo reoperation on an urgent basis. With any biological device there will be a number of patients who defy the usual expected result and do extraordinarily well for long periods of time. I even recall a few patients with the formalin-fixed, porcine valves prior to the glutaraldehyde era (which were a total disaster) in whom somehow the collagen was stabilized intrinsically and the valve functioned relatively well; a few patients had these valves for a considerable period of time. I believe we should follow up all patients with pericardial, porcine, or homograft valves extremely closely. I do not think 12 months is a close enough referral for routine follow-up visits, particularly when patients are at least 3 years after operation for pericardial valves and may be 8 years after operation for porcine and homograft valves. Surveillance should be increased to 3- to 6-month intervals after certain follow-up periods, and examina-

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tions should include echocardiograms. At the first sign of any new murmur or any change in symptomatology suggesting the stenosis of that valve, I think the patient should be submitted for a reoperation.

Recently, we read of the convexo-concave Björk-Shiley valve problem in the media, a more complicated problem because when failure occurs, however rare, it is sudden and almost always fatal. The Shiley Company now says replacing the valve is not necessary because the risk is small, estimated at 29/100,000 per year in the vulnerable mitral sizes. I personally disagree. I would feel justified in re-replacing this valve in any patient who expresses concern about this risk, regardless of symptomatology, providing there is evidence of a low risk for valve reoperations in the surgical unit proposing to replace the valve.

With new operative and perfusion technology, including membrane oxygenators, providing better and safer treatment of patients undergoing reoperations, and with better valve devices, the results of valve re-replacement should be similar to those of primary valve replacement. The most important factor in obtaining good results is not waiting too long before considering reoperation. We are grateful again to the Padova group for bringing these kind of data about biological valves to our attention, and for reinforcing our attention and vigilance for all patients with heart valves, particularly those made of pericardium.

Reference

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Magnesium Ion Is Beneficial in Hypothermic Crystalloid Cardioplegia

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The role of magnesium ion and its relation to the calcium concentration of cardioplegic solutions was reexamined in this study. Isolated rat hearts were used with an oxygenated modified Krebs-Henseleit bicarbonate buffer as perfusion medium. The hearts were arrested for 20 minutes at 37°C or 90 minutes at 24°C. Treatment groups received one dose of nine possible cardioplegic solutions containing magnesium (0, 1.2, or 15 mmol/L) and calcium (0.05, 1.5, or 4.5 mmol/L). Ninety-six percent of the 75 magnesium-treated hearts recovered, regardless of the calcium concentration, in contrast to a 52% recovery rate in the 69 hearts that did not receive magnesium. The addition of 15 mmol/L Mg^{2+} to a cardioplegic solution containing no magnesium but 0.05 mmol/L Ca^{2+} significantly increased ($p < 0.01$) the percent recovery of the following parameters of cardiac function: systolic pressure, 74% to 93% (37°C), 64% to 98% (24°C); cardiac output, 76% to 101% (37°C), 71% to 102% (24°C); stroke work, 64% to 104% (37°C), 52% to 99% (24°C); and adenosine triphosphate level, 75% to 83% (37°C), 58% to 90% (24°C). There were significant reductions ($p < 0.03$) in percent recovery (37°C and 24°C) of cardiac output, stroke work, and adenosine triphosphate level in the groups that contained 0 or 15 mmol/L Mg^{2+} as the calcium concentration was increased from 0.05 to 4.5 mmol/L. Significant progressive augmentation of ventricular recovery and decreased overall mortality is produced at 37° and 24°C with cardioplegia containing high levels of magnesium and low levels of calcium. These data demonstrate the importance of the Mg^{2+}/Ca^{2+} relation in an oxygenated crystalloid solution with a pH of 7.45, carbon dioxide tension of 40 mm Hg, and oxygen tension of 750 mm Hg containing 142 mmol/L Na^{+}.

(Ann Thorac Surg 1991;51:359–67)

Inclusion of magnesium ion in cardioplegic solutions has been shown to increase ventricular performance after varying intervals of ischemia and reperfusion [1–4]. The addition of magnesium has not been universally accepted, despite these reports of improved myocardial preservation. This is in contrast to the inclusion of calcium, which has been almost universally accepted [5, 6]. The specific interaction between magnesium and calcium has not yet been delineated. However it has been proposed that magnesium acts as a physiological calcium channel blocker [7]. The hypothesis of this report is that cardioplegia containing magnesium ion increases postischemic myocardial performance under normothermic and hypothermic conditions and that magnesium will antagonize the negative effects of calcium. This study used isolated rat hearts to investigate the physiological and biochemical consequences of three different magnesium concentrations, each with three calcium concentrations under normothermic and hypothermic ischemic conditions.

Material and Methods

Experimental Model

The preparation used was that of an isolated, ex vivo, perfused, working left heart. This model is nonphysiological because neuronal and hormonal control as well as the effects of circulating catecholamines are lost, but it is still a useful method of initial evaluation of the action of pharmacologic agents upon the heart. Hearts were obtained from male Sprague-Dawley rats weighing 300 to 450 g. Each animal was injected with 1,000 units of heparin (intraperitoneally) and then anesthetized with 4 mL of a 7.2% solution of chloral hydrate (intraperitoneally) (Fisher Scientific, Fairlawn, NJ). The heart was rapidly excised and placed in a modified Krebs-Henseleit bicarbonate buffer solution at 2°C (Table 1) and was prepared according to a modified Langendorff technique [8].

The aorta was cannulated, and the heart was mounted on a Langendorff apparatus. Retrograde perfusion was started with modified Krebs-Henseleit bicarbonate buffer solution at 37°C. Buffer flowed freely into the aortic root at a hydrostatic pressure of 80 cm for 15 minutes to allow recovery and development of a steady nonworking state. Conversion to a working preparation was achieved by placing a second perfusion cannula into the left atrium and infusing buffer solution at 20 cm of hydrostatic pressure. The left ventricle ejected against a hydrostatic

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Table 1. Composition of Modified Krebs-Henseleit Bicarbonate Buffer Solution and Nine Different Cardioplegic Solutions

Ingredient	Buffer	Cardioplegic Solution (mmol/L) 1	2	3	4	5	6	7	8	9
$MgSO_4$ (mmol/L)	1.20	0.00	0.00	0.00	1.20	1.20	1.20	15.00	15.00	15.00
$CaCl_2$ (mmol/L)	1.50	0.05	1.50	4.50	0.05	1.50	4.50	0.05	1.50	4.50
KCl (mmol/L)	4.50	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00

Each solution also contained the following: NaCl, 116.00 mmol/L; $NaHCO_3$, 25.00 mmol/L; NaH_2PO_4, 0.80 mmol/L; heparin, 6.00 mg/L; glucose, 15.00 mmol/L; insulin, 0.40 U/L; glycine, 25.24 mg/L; lysine, 69.23 mg/L; valine, 22.03 mg/L; L-alanine, 29.05 mg/L; L-arginine, 20.73 mg/L; L-asparagine, 8.99 mg/L; L-aspartic acid, 1.86 mg/L; L-cysteine, 7.88 mg/L; L-glutamic acid, 17.65 mg/L; L-glutamine, 95.27 mg/L; L-histidine, 44.97 mg/L; L-isoleucine, 14.17 mg/L; L-leucine, 21.77 mg/L; L-methionine, 8.05 mg/L; L-phenylalanine, 11.40 mg/L; L-proline, 12.43 mg/L; L-serine, 25.96 mg/L; L-threonine, 24.17 mg/L; L-tryptophan, 10.21 mg/L; and L-tyrosine, 12.50 mg/L, with a carbon dioxide tension of 40 mm Hg, oxygen tension of 750 mm Hg, pH of 7.45, and osmolarity of 290.0 mosm/L.

pressure of 80 cm into a compliance chamber with a 2.5 mL air capacity. The pulmonary artery was widely opened to allow for drainage of coronary sinus effluent. Three temperature circuits permitted buffer, cardioplegia, and each heart to be maintained at any desired temperature. All fluid entering the heart was filtered through 0.2-μm filters (Pall Biomedical Inc, Fajardo, PR). A thermistor (Electromedics, Inc, Englewood, CA) was placed on the left ventricle and the myocardial temperature was kept within 0.5°C of the desired temperature. All buffer and cardioplegic solutions were prepared by the National Institutes of Health Media Service on a weekly basis and, once added to the apparatus, were gassed continuously with a mixture of 95% oxygen and 5% carbon dioxide. This resulted in a solution with a measured osmolarity of 297 mosm/L, pH of 7.40 to 7.50, carbon dioxide tension of 35 to 45 mm Hg, and oxygen tension greater than 750 mm Hg (Radiometer ABL3, Copenhagen, Denmark). No attempt to correct for the varying osmolarity of the solutions was made as Hearse and associates [1] have previously shown that there were minimal differences in osmolarity over the concentration ranges used in this experiment.

Preischemic measurements were made after 15 minutes of perfusion in the working mode. Aortic and coronary flow were measured by timed collection into graduated cylinders. Systolic, diastolic, and mean pressure were recorded on an electrostatic recorder (Gould ES2000, Gould Inc, Oxnard, CA), and pressure data were obtained from pressure transducers (Gould P23) placed in the aortic outflow chamber. Heart rate was obtained from the pressure tracing. A heart was rejected if the heart rate was less than 200 beats/min, cardiac output was less than 40 mL/min, or if the coronary to aortic flow ratio was greater than 0.60, indicating serious iatrogenic injury during preparation.

Ischemic injury was induced by clamping the left atrial cannula and perfusing the aortic root with 20 mL of 37°C hyperkalemic cardioplegic solution (see Table 1) at 80 cm hydrostatic pressure. The hearts were given cardioplegia and maintained at 37°C for 20 minutes or were given 24°C cardioplegia and maintained at 24°C throughout a 90-minute ischemia period. During the period of ischemia the heart was vented through the left atrial cannula. The heart was reperfused with buffer solution through the aortic root for 15 minutes in the nonworking mode to allow washout of metabolites and rewarming. The heart was then placed in the working mode and postischemic measurements were made after 20 minutes. The buffer solution was recirculated only when the heart was in the working mode. The beating heart was frozen with stainless steel Wollenberger tongs previously cooled to −70°C in liquid nitrogen. The distal portion of the heart was crushed and stored at −70°C. Analysis for adenosine triphosphate (ATP), adenosine diphosphate, adenosine monophosphate, and nicotinamide adenine dinucleotide content was performed within 24 hours by high-performance liquid chromatography.

Adenosine Triphosphate Determination

Heart tissue samples of 25 mg were pulverized and homogenized in 6% perchloric acid at 0°C. After 30 minutes of extraction at 0°C, the samples were centrifuged for 10 minutes at 10,000 rpm and 0°C. The supernatant was neutralized to pH 7.0 by addition of KOH. The resulting fluid was then centrifuged for 5 minutes at 10,000 rpm and 0°C. The supernatant was again drawn off and filtered through a Pall 0.2-μm millipore filter before nucleotide determination [9]. The protein pellets remaining after the perchloric acid extraction were solubilized by heating in 0.5 N NaOH at 90°C for 1 hour. After thorough mixing, the total intracellular soluble protein content was determined by the method of Lowry and associates [10].

Nucleotide analyses were carried out on a Waters 510 HPLC (Millipore Corp, Venture, CA) with a variable-wavelength ultraviolet detector set at 254 nm. The separation of 10-μL samples was performed on a Hypersel ODS C-18 150 × 4.6-mm reverse-phase column (Keystone Scientific, Inc, State College, PA) at an eluent flow rate of 1.0 mL/min. The elution technique consisted of a gradient of methanol in an ammonium phosphate buffer (75 mmol/L, pH 5.75), with an analysis time, including column regeneration, of 16 minutes. Values were expressed as micromoles/gram of total intracellular soluble protein. Standards of adenosine monophosphate, adenosine diphosphate, ATP, and nicotinamide adenine dinucleotide were obtained for calibration of sample nucleotides (Sigma Chemical Company, St. Louis, MO). High-performance liquid chromatography–grade ammonium

Table 2. Percentage of Working Hearts After Ischemic Arrest

Cardioplegia Group	[Mg] (mmol/L)	[Ca] (mmol/L)	n	Working After Ischemia	
				No.	%
20 minutes of ischemic arrest at 37°C					
1	0.00	0.05	9	6	67
2	0.00	1.50	12	6	50
3	0.00	4.50	14	6	43
4	1.20	0.50	6	6	100
5	1.20	1.50	6	6	100
6	1.20	4.50	7	6	86
7	15.00	0.05	6	6	100
8	15.00	1.50	6	6	100
9	15.00	4.50	6	6	100
90 minutes of ischemic arrest at 24°C					
1	0.00	0.05	11	6	54
2	0.00	1.50	12	6	50
3	0.00	4.50	11	6	54
4	1.20	0.05	6	6	100
5	1.20	1.50	7	6	86
6	1.20	4.50	7	6	86
7	15.00	0.05	6	6	100
8	15.00	1.50	6	6	100
9	15.00	4.50	6	6	100

Table 3. Average Values of Rat Heart Adenosine Triphosphate Before Ischemic Arrest

Time	n	[ATP] ± SEM
Frozen in chest	5	32.96 ± 2.67
Excised and frozen	6	30.78 ± 0.63
After 1 minute of perfusion	6	36.13 ± 1.58
After 5 minutes of perfusion	10	35.72 ± 2.01
After 15 minutes of perfusion	9	42.66 ± 2.20
After 30 minutes of perfusion[a]	8	42.50 ± 1.90

[a] Second 15 minutes in working mode.

ATP = adenosine triphosphate (μmol/g protein); SEM = standard error of the mean.

phosphate was obtained from Fisher Scientific Company (Fairlawn, NJ).

Experimental Design

Nine experimental cardioplegic solutions and two temperatures were studied. All of the cardioplegic solutions contained 25.0 mmol/L potassium. Three groups contained either 0, 1.2, or 15 mmol/L magnesium sulfate. Each group was further broken down into three subgroups containing either 0.05, 1.5, or 4.5 mmol/L calcium chloride. A minimum of 6 rat hearts comprised each

Table 4. Average[a] Function After 20 Minutes of Ischemic Arrest at 37°C

Variable	Group								
	1	2	3	4	5	6	7	8	9
[Mg]	0.00	0.00	0.00	1.20	1.20	1.20	15.00	15.00	15.00
[Ca]	0.05	1.50	4.50	0.05	1.50	4.50	0.05	1.50	4.50
HR									
Pre	220.9 ± 11.2	244.4 ± 8.1	298.4 ± 18.9	204.3 ± 31.6	275.9 ± 19.6	267.2 ± 16.4	265.3 ± 23.1	272.7 ± 13.6	246.3 ± 12.1
Post	233.0 ± 14.5	267.6 ± 6.0	291.8 ± 24.0	203.7 ± 4.7	267.2 ± 20.6	257.5 ± 16.3	258.5 ± 22.6	253.7 ± 13.5	244.4 ± 13.8
AF									
Pre	51.2 ± 5.0	55.8 ± 4.1	57.3 ± 2.7	57.3 ± 9.1	74.4 ± 3.4	62.3 ± 7.0	59.2 ± 5.5	44.4 ± 1.9	55.3 ± 6.1
Post	32.8 ± 5.6	31.0 ± 4.2	23.7 ± 2.8	48.1 ± 6.3	55.4 ± 2.0	42.8 ± 5.1	57.7 ± 5.9	41.8 ± 2.4	50.0 ± 5.2
CF									
Pre	21.6 ± 2.3	20.7 ± 3.6	22.4 ± 2.6	31.1 ± 8.8	18.2 ± 2.9	19.2 ± 2.3	27.9 ± 2.0	20.2 ± 2.5	18.3 ± 3.1
Post	23.2 ± 1.9	24.7 ± 3.7	24.5 ± 3.4	24.1 ± 3.4	20.3 ± 2.6	20.0 ± 5.4	25.8 ± 2.2	18.8 ± 2.0	19.6 ± 3.5
SP									
Pre	87.7 ± 4.3	91.4 ± 4.9	96.9 ± 9.3	73.6 ± 8.0	96.5 ± 6.8	87.2 ± 9.2	90.2 ± 3.7	79.3 ± 3.3	89.7 ± 8.7
Post	65.4 ± 7.1	62.8 ± 6.3	64.0 ± 5.7	65.3 ± 7.2	80.2 ± 4.5	75.3 ± 7.9	85.0 ± 3.2	74.1 ± 3.6	83.3 ± 7.7
DP									
Pre	29.3 ± 3.8	30.9 ± 4.1	34.7 ± 1.4	32.4 ± 4.4	28.0 ± 6.7	22.8 ± 2.5	36.5 ± 2.9	35.9 ± 2.1	29.1 ± 5.8
Post	35.6 ± 3.2	38.4 ± 5.3	43.1 ± 3.6	34.4 ± 1.9	29.6 ± 6.6	24.2 ± 2.2	39.3 ± 2.0	35.7 ± 1.5	30.3 ± 5.2
ATP									
Pre	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9
Post	34.2 ± 0.7	32.0 ± 2.5	29.8 ± 0.9	34.7 ± 0.7	32.9 ± 0.8	31.6 ± 0.7	38.9 ± 0.9	34.8 ± 1.0	33.2 ± 1.1

[a] n = 6 hearts in each group; values expressed as mean ± standard error of the mean.

AF = aortic flow (mL/min); ATP = adenosine triphosphate (μmol/g protein); Ca = calcium (mmol/L); CF = coronary flow (mL/min); DP = diastolic pressure (mm Hg); HR = heart rate (beats/min); Mg = magnesium (mmol/L); pre = before ischemia; post = after ischemia; SP = systolic pressure (mm Hg).

Table 5. Average[a] Function After 90 Minutes of Ischemic Arrest at 24°C

Variable	Group 1	2	3	4	5	6	7	8	9
[Mg]	0.00	0.00	0.00	1.20	1.20	1.20	15.00	15.00	15.00
[Ca]	0.05	1.50	4.50	0.05	1.50	4.50	0.05	1.50	4.50
HR									
Pre	215.9 ± 3.0	265.5 ± 16.4	256.6 ± 18.3	275.9 ± 15.4	271.3 ± 22.7	234.5 ± 14.1	269.0 ± 22.3	282.4 ± 21.3	285.4 ± 19.7
Post	237.7 ± 5.0	317.7 ± 17.1	257.1 ± 19.0	286.0 ± 13.8	292.2 ± 21.6	279.8 ± 11.9	253.3 ± 21.2	288.3 ± 21.0	274.3 ± 19.9
AF									
Pre	55.6 ± 4.8	58.9 ± 6.1	58.5 ± 7.4	57.3 ± 5.3	62.2 ± 7.3	72.1 ± 5.9	59.2 ± 6.2	51.5 ± 4.9	57.0 ± 5.3
Post	29.2 ± 3.0	30.5 ± 3.1	30.0 ± 4.7	44.1 ± 3.5	44.1 ± 5.2	45.0 ± 4.4	60.5 ± 6.1	46.5 ± 4.5	47.3 ± 5.5
CF									
Pre	21.4 ± 1.5	24.1 ± 2.4	19.7 ± 2.1	20.7 ± 2.1	23.4 ± 4.2	23.7 ± 3.9	25.6 ± 2.5	21.6 ± 3.2	23.0 ± 2.8
Post	25.3 ± 3.0	30.4 ± 3.1	21.6 ± 2.8	23.8 ± 2.1	25.5 ± 4.3	28.3 ± 4.5	24.6 ± 2.1	21.9 ± 3.4	21.7 ± 2.8
SP									
Pre	81.4 ± 5.2	61.9 ± 4.5	69.6 ± 2.9	68.0 ± 4.2	62.2 ± 3.2	71.7 ± 3.8	70.6 ± 4.4	73.9 ± 5.2	77.7 ± 6.1
Post	52.2 ± 3.4	34.7 ± 2.1	37.0 ± 3.2	52.6 ± 4.4	46.0 ± 3.4	51.5 ± 1.3	69.2 ± 3.9	66.9 ± 4.7	68.1 ± 5.9
DP									
Pre	36.8 ± 1.5	25.7 ± 3.2	26.3 ± 3.8	25.5 ± 1.9	25.4 ± 3.2	31.6 ± 1.6	32.2 ± 4.2	35.6 ± 3.2	36.6 ± 3.3
Post	42.5 ± 1.6	28.3 ± 3.8	26.7 ± 2.8	30.1 ± 2.5	27.4 ± 2.7	34.3 ± 2.1	30.3 ± 4.3	36.0 ± 3.5	36.8 ± 3.2
ATP									
Pre	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9	45.5 ± 1.9
Post	26.4 ± 0.7	22.7 ± 0.9	22.7 ± 0.7	34.6 ± 0.7	31.3 ± 0.3	31.7 ± 0.4	41.0 ± 0.2	40.5 ± 0.4	38.4 ± 0.2

[a] n = 6 hearts in each group; values expressed as mean ± standard error of the mean.

AF = aortic flow (mL/min); ATP = adenosine triphosphate (μmol/g protein); Ca = calcium (mmol/L); CF = coronary flow (mL/min); DP = diastolic pressure (mm Hg); HR = heart rate (beats/min); Mg = magnesium (mmol/L); pre = before ischemia; post = after ischemia; SP = systolic pressure (mm Hg).

subgroup. The cardioplegic solutions contained the same ingredients as the modified Krebs-Henseleit buffer solution, with the exception of the changes in potassium, magnesium, and calcium outlined in Table 1. The ischemic times of 20 and 90 minutes were chosen because preliminary research demonstrated that they would produce serious ischemic injury. This preparation resulted in a 50% mortality in the control groups (1, 4, 7) after the ischemic insult. An approximately 60% morbidity (60% of preischemic values) also resulted in those hearts that survived (Table 2). All of the animals used received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Statistical Analysis

Each measured (aortic flow, coronary flow, heart rate, systolic pressure, and diastolic pressure) or calculated (cardiac output, stroke volume, left ventricular stroke work) variable was determined three times approximately 1 minute apart just before ischemic arrest and again at the end of the experiment. The mean percent recovery of the preischemic values was determined for each heart and for each group of 6 hearts. All statistical analyses were performed on the percent recovery values. The determination of adenine nucleotides was performed twice for each sample and the percent recovery determined. A group of control rats, which were killed before ischemic arrest, provided the preischemic values (Table 3). Two-way and three-way analysis of variance was performed. Significant intergroup interactions were subjected to one-way analysis of variance with Sheffé probability testing. Significance was determined at $p < 0.05$. All data were expressed as the mean ± the standard error of the mean. Data analysis was performed using Ab-Stat Software (Anderson-Bell Corp, Parker, CO) and Excel (Microsoft Corp, Redmond, WA) on an IBM P/S 2 model 70 computer.

Results

Mortality was defined as a heart that did not have any aortic flow after ischemic arrest (excluding coronary flow) regardless of whether or not a systolic pressure or heart rate was maintained. Ninety-six percent of the 75 hearts that received magnesium-containing cardioplegia performed work after ischemic arrest, whereas only 52% of the 69 control hearts that did not receive magnesium-containing cardioplegia performed postischemic work (see Table 2). Increasing calcium concentration was correlated with higher mortality. Tables 4 and 5 show the average preischemic and postischemic cardiac variables after normothermic and hypothermic ischemic arrest.

Table 6. Average[a] Percent Recovery of Function After 20 Minutes of Ischemic Arrest at 37°C

	Group								
Variable	1	2	3	4	5	6	7	8	9
[Mg]	0.00	0.00	0.00	1.20	1.20	1.20	15.00	15.00	15.00
[Ca]	0.05	1.50	4.50	0.05	1.50	4.50	0.05	1.50	4.50
HR	106 ± 6	110 ± 4	98 ± 4	89 ± 4	97 ± 1	96 ± 2	96 ± 1	93 ± 1	99 ± 2
AF	62 ± 5	55 ± 4	41 ± 4	74 ± 10	75 ± 2	69 ± 3	101 ± 1	95 ± 5	91 ± 3
CF	109 ± 4	123 ± 10	110 ± 9	116 ± 9	114 ± 3	105 ± 4	100 ± 4	95 ± 5	103 ± 4
SP	74 ± 5	68 ± 5	68 ± 7	80 ± 6	84 ± 2	87 ± 4	93 ± 6	93 ± 1	93 ± 2
DP	126 ± 3	125 ± 9	124 ± 9	117 ± 9	107 ± 3	108 ± 1	108 ± 1	100 ± 3	107 ± 4
CO	76 ± 3	72 ± 3	60 ± 5	83 ± 9	82 ± 1	77 ± 2	101 ± 2	95 ± 2	94 ± 2
SV	72 ± 2	66 ± 3	61 ± 3	97 ± 6	85 ± 1	80 ± 1	105 ± 2	102 ± 3	95 ± 2
LVSW	64 ± 4	54 ± 3	50 ± 2	90 ± 2	72 ± 2	70 ± 2	104 ± 2	95 ± 3	92 ± 2
ATP	75 ± 6	70 ± 6	65 ± 2	76 ± 2	72 ± 2	69 ± 1	83 ± 2	76 ± 2	73 ± 2

[a] n = 6 hearts in each group; values expressed as mean ± standard error of the mean.

AF = aortic flow; ATP = adenosine triphosphate; Ca = calcium (mmol/L); CF = coronary flow; CO = cardiac output; DP = diastolic pressure; HR = heart rate; LVSW = left ventricular stroke work; Mg = magnesium (mmol/L); SP = systolic pressure; SV = stroke volume.

Tables 6 and 7 show the average percent recovery of preischemic values after normothermic and hypothermic ischemic arrest.

Intra-Calcium Concentration Relationships

Hearts were treated with 15 versus 0 mmol/L Mg^{2+} within each of the three calcium concentrations. Fifteen versus 0 mmol/L Mg^{2+} with 0.05 mmol/L Ca^{2+} increased ($p < 0.01$) the percent recovery of systolic pressure (74% to 93% at 37°C, 64% to 98% at 24°C), cardiac output (76% to 101% at 37°C, 71% to 102% at 24°C), stroke work (64% to 104% at 37°C, 52% to 99% at 24°C), and [ATP] (75% to 83% at 37°C, 58% to 90% at 24°C). These same relationships were observed with the addition of 1.2 mmol/L Mg^{2+} at 24°C, but only stroke work was increased at 37°C. Decreases ($p < 0.01$) in the percent recovery of heart rate (106% to 96% at 37°C, 110% to 94% at 24°C) and diastolic pressure (126% to 108% at 37°C, 116% to 93% at 24°C) were seen with 15 mmol/L Mg^{2+}. With the addition of 1.2 mmol/L Mg^{2+}, heart rate was decreased ($p < 0.01$) at 24°C and diastolic pressure was decreased ($p < 0.01$) at 37°C (Fig 1).

Fifteen versus 0 mmol/L Mg^{2+} with 1.5 mmol/L Ca^{2+} increased the percent recovery ($p < 0.01$) of systolic pressure (68% to 93% at 37°C, 59% to 90% at 24°C), cardiac

Table 7. Average[a] Percent Recovery of Function After 90 Minutes of Ischemic Arrest at 24°C

	Group								
Variable	1	2	3	4	5	6	7	8	9
[Mg]	0.00	0.00	5.00	1.20	1.20	1.20	15.00	15.00	15.00
[Ca]	0.05	1.50	4.50	0.05	1.50	4.50	0.05	1.50	4.50
HR	116 ± 3	115 ± 3	100 ± 3	103 ± 1	108 ± 1	120 ± 6	94 ± 1	102 ± 1	96 ± 1
AF	53 ± 3	50 ± 4	50 ± 3	77 ± 2	70 ± 1	62 ± 2	103 ± 2	90 ± 1	82 ± 2
CF	116 ± 6	117 ± 3	110 ± 2	116 ± 5	111 ± 5	120 ± 3	99 ± 5	101 ± 4	95 ± 6
SP	64 ± 3	59 ± 3	53 ± 4	77 ± 4	73 ± 2	72 ± 3	98 ± 1	90 ± 1	87 ± 1
DP	116 ± 4	114 ± 10	105 ± 7	118 ± 3	109 ± 4	108 ± 3	93 ± 1	100 ± 1	101 ± 3
CO	71 ± 3	69 ± 3	65 ± 2	87 ± 1	81 ± 1	76 ± 2	102 ± 1	93 ± 1	85 ± 2
SV	64 ± 2	60 ± 2	65 ± 1	84 ± 2	75 ± 1	63 ± 3	108 ± 2	91 ± 1	89 ± 2
LVSW	52 ± 3	39 ± 4	30 ± 7	75 ± 5	56 ± 3	51 ± 2	99 ± 1	83 ± 2	79 ± 3
ATP	58 ± 1	50 ± 2	50 ± 1	76 ± 1	68 ± 1	69 ± 1	90 ± 1	89 ± 1	84 ± 0

[a] n = 6 hearts in each group; values expressed as mean ± standard error of the mean.

AF = aortic flow; ATP = adenosine triphosphate; Ca = calcium (mmol/L); CF = coronary flow; CO = cardiac output; DP = diastolic pressure; HR = heart rate; LVSW = left ventricular stroke work; Mg = magnesium (mmol/L); SP = systolic pressure; SV = stroke volume.

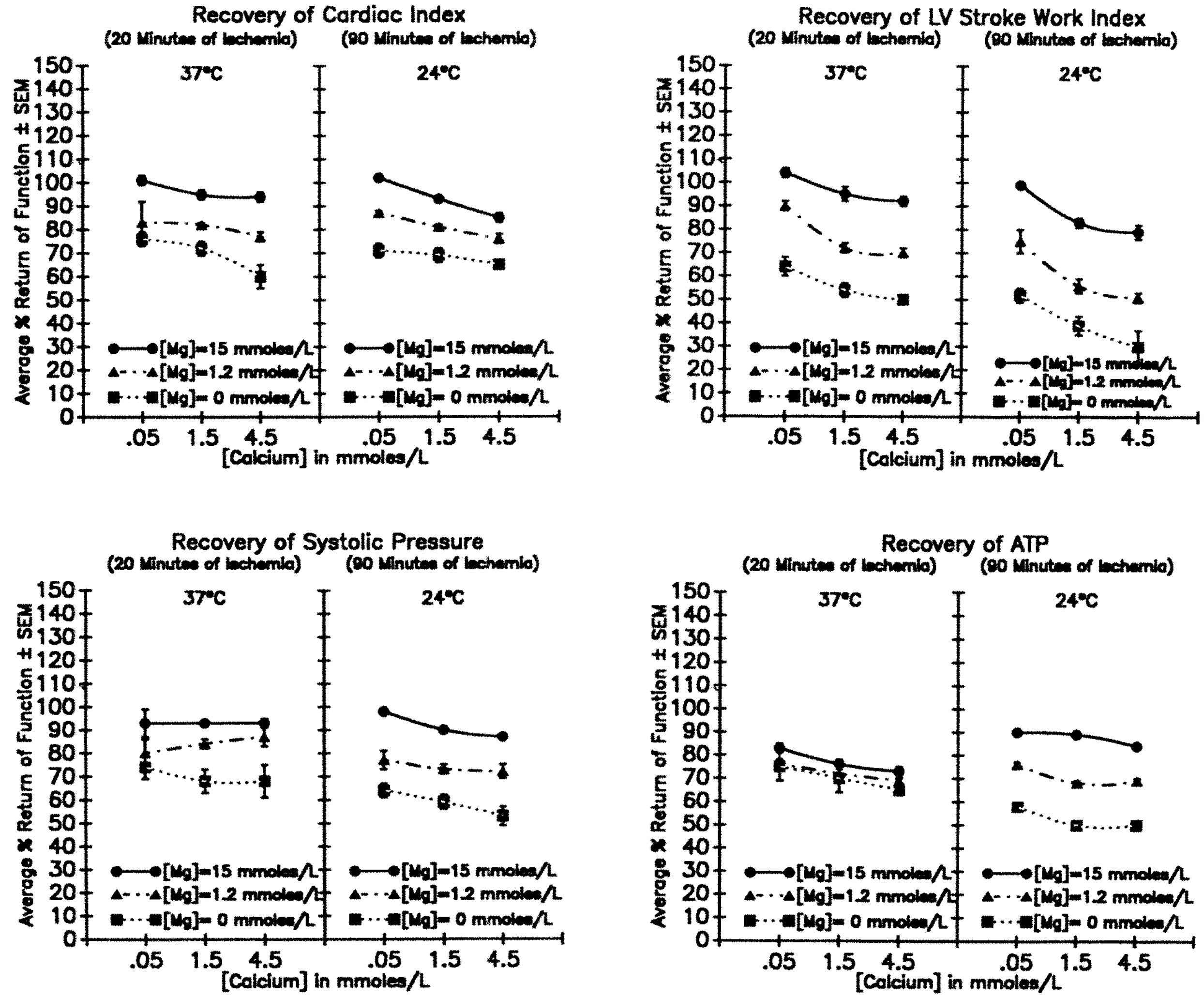

Fig 1. Percent recovery of preischemic values after the administration of normothermic (37°C) and hypothermic (24°C) cardioplegia (n = 6 for each point). Cardiac index, left ventricular stroke work index, systolic pressure, and adenosine triphosphate (ATP) *concentration all increased (*p *< 0.01) when comparing groups with 0 versus 15 mmol/L* Mg^{2+} *regardless of calcium concentration at 37°C and 24°C. (LV = left ventricular;* SEM *= standard error of the mean.)*

output (72% to 95% at 37°C, 69% to 93% at 24°C), stroke work (54% to 95% at 37°C, 39% to 83% at 24°C), and [ATP] (70% to 76% at 37°C, 50% to 89% at 24°C) and decreased ($p < 0.01$) the percent recovery of heart rate (110% to 93% at 37°C, 115% to 102% at 24°C) and diastolic pressure (125% to 100% at 37°C, 114% to 100% at 24°C). These same relationships were also significant with the addition of 1.2 mmol/L Mg^{2+} to a magnesium-free solution.

Fifteen versus 0 mmol/L Mg^{2+} with 4.5 mmol/L Ca^{2+} increased ($p < 0.01$) the percent recovery of systolic pressure (68% to 93% at 37°C, 53% to 87% at 24°C), cardiac output (60% to 94% at 37°C, 65% to 85% at 24°C), stroke work (50% to 92% at 37°C, 30% to 79% at 24°C), and [ATP] (65% to 73% at 37°C, 50% to 84% at 24°C) and decreased ($p < 0.01$) the percent recovery of diastolic pressure (124% to 107% at 37°C only). These same relationships also existed after the addition of 1.2 mmol/L of Mg^{2+} except for recovery of ATP at 37°C and heart rate and diastolic pressure at 24°C.

Intra-Magnesium Concentration Relationships

Hearts were treated with 4.5 versus 0.05 mmol/L Ca^{2+} within each of the three magnesium concentrations. A concentration of 4.5 versus 0.05 mmol/L Ca^{2+} with 0 mmol/L Mg^{2+} decreased ($p < 0.03$) the percent recovery of systolic pressure (64% to 53% at 24°C only), stroke work (64% to 50% at 37°C, 52% to 30% at 24°C), and [ATP] (75% to 65% at 37°C, 58% to 50% at 24°C).

A concentration of 4.5 versus 0.05 mmol/L Ca^{2+} with 1.2 mmol/L Mg^{2+} decreased ($p < 0.03$) the percent recovery of cardiac output (83% to 77% at 37°C, 87% to 76% at 24°C), stroke work (90% to 70% at 37°C, 75% to 51% at 24°C), and [ATP] (76% to 69% at 37°C, 76% to 69% at 24°C).

A concentration of 4.5 versus 0.05 mmol/L Ca^{2+} with 15 mmol/L Mg^{2+} decreased ($p < 0.03$) the percent recovery of systolic pressure (98% to 87% at 24°C only), cardiac output 101% to 94% at 37°C, 102% to 85% at 24°C), and stroke work (104% to 92% at 37°C, 99% to 79% at 24°C).

Comment

The results of this study show that increasing the magnesium concentration in a crystalloid cardioplegic solution from 0 to 15 mmol/L (with either 0.05, 1.5, or 4.5 mmol/L Ca^{2+}) resulted in significantly improved ventricular performance and preservation of ATP concentrations after normothermic and hypothermic ischemic arrest. Increasing the calcium concentration from 0.05 to 4.5 mmol/L (with either 0, 1.2, or 15 mmol/L Mg^{2+}) had a detrimental effect on ventricular performance. The negative effects of a high-calcium solution were not completely ameliorated with 15 mmol/L Mg^{2+}, and function still declined after the addition of calcium to any particular magnesium-containing solution. However incremental increases in magnesium concentration had a more profound positive effect on postischemic ventricular function than did decremental changes in calcium concentration.

Hearts treated with cardioplegic solution containing magnesium achieved maximal cardiac output and heart rate after a 20-minute postischemic working period. Maximal function of the hearts not treated with magnesium was observed within minutes after rewarming. The magnesium-treated groups had a slow but steady improvement of cardiac function over time. This was important in allowing the latter hearts to regain energy stores and repair intracellular damage. Regardless of the type of cardioplegic solution used to achieve cardioplegic arrest, there needs to be a rationale for all of the ingredients that are included in or excluded from the solution. Magnesium and calcium ion are extremely important because they are the most abundant intracellular cations, excluding potassium, and are critical to almost all intracellular reactions. Calcium ion is the main regulatory factor of the myocardial contraction apparatus and magnesium is a cofactor of the magnesium-dependent ATPase enzyme, which provides energy for myocardial contraction and allows the sodium-potassium membrane pumps to maintain intracellular hemostasis.

The combinations of magnesium and calcium ion that produced the best postischemic ventricular function were tenfold greater and less, respectively, than normal serum levels. A cardioplegic solution that contains electrolytes and other substrates in physiological concentrations would on initial inspection appear to be superior; however, cardioplegic ischemic arrest and reperfusion is not a physiological phenomenon and, as these data show, normal serum concentrations of electrolytes do not necessarily produce improved postischemic ventricular function.

Hearse and associates [1] have shown that a cardioplegic solution with 16 mmol/L of Mg^{2+} and 1.2 mmol/L Ca^{2+} provided significant postischemic ventricular protection at 37°C and 28°C. The current results confirm those of Hearse and associates but go further by showing that magnesium provides increased protection down to at least 24°C. Reynolds and co-workers [2] recently evaluated the effects of multidose magnesium-containing cardioplegic solution with 0.1 mmol/L Ca^{2+} and 16 mmol/L Mg^{2+} at 8°C. This resulted in increased postischemic aortic flow and intracellular creatine phosphate levels, although no changes in ATP concentration could be demonstrated. The current results differ from those of Reynolds and co-workers in that significant increases in [ATP] were observed in this study with increasing magnesium concentration, especially after hypothermic ischemia arrest. This provides functional as well as biochemical evidence of ventricular protection. The [ATP] measured in this study was expressed in terms of micrograms per gram of total soluble intracellular protein, which is independent of intracellular water gain and is a more sensitive method to measure the concentration of ATP.

Hypothermia is an important adjunct to cardioplegia and can provide significant protection to the ischemic myocardium. Hypothermia is protective against the calcium paradox when infusion of the calcium-free media is begun at 28° to 30°C [6], but decreasing the temperature to 4°C during reperfusion does not prevent the calcium paradox [6] or prevent injury caused by reperfusate containing a high level of calcium [5]. This protective effect during ischemia may be owing to a phase transition between a fluid and gellike state of the membrane [5], thus preventing leakage of electrolytes into and out of the cell. Magnesium-containing cardioplegia continues to exert a positive effect below 28°C that is additive to that of hypothermia. This is not the case with a calcium antagonist such as verapamil, which is ineffective in preventing ischemic damage when administered in hypothermic cardioplegic solutions [11].

Ischemic injury may be characterized in part by the loss of ATP stores, intracellular acidosis, free radical formation, and intracellular edema. All of these disrupt the normal internal milieu of the cell during ischemia and lead to even greater damage on reperfusion. The damage that occurs during the calcium paradox is probably only a more severe form of the damage that occurs with ischemic arrest in the presence of calcium.

The exact mechanism of magnesium's action is not known at this time, but it probably acts through two mechanisms. The first action is that of a cofactor in all energy-requiring reactions. Loss of intracellular cellular magnesium is one of the earliest signs of myocardial injury with a twofold increase in magnesium efflux occurring during hypoxia [12]. During cardioplegic arrest mechanical contraction of the sarcomere is not needed; however, continued operation of the sodium-potassium exchange membrane pumps does require the presence of ATP and magnesium. As ATP is utilized and production is slowed during ischemia, one would expect to observe a loss of free magnesium from the cell. Tani and colleagues [13] have shown that intracellular sodium concentration increases during ischemia and that the higher the calcium concentration in the reperfusing solution, the higher the exchange of intracellular sodium for calcium and the more the resulting cellular injury. Excessive calcium entry through the Na^+/Ca^{2+} exchange pump is one of the major factors that determine the recovery of function during reperfusion. Murphy and associates [14] have shown that dichlorobenzamil, which is a blocker of this pump, reduced the calcium influx significantly when given during a 30-minute reperfusion period.

The second proposed method of action is that of a calcium antagonist [7]. White and Hartzell [15], using voltage clamp experiments, have shown that magnesium inhibits the opening of the voltage-dependent calcium channel and does so more during periods of channel phosphorylation or at relatively high energy states within the cell. When energy is less available, as during ischemia, calcium entry into the cell is increased. Whether this occurs by actual blockade of these channels or merely modulation of conductivity is not known. Magnesium has also been shown to block the release of calcium from the sarcoplasmic reticulum, thereby leading to lower cytosolic levels [16] and also to increase the uptake of calcium into the sarcoplasmic reticulum [17]. Favaron and Bernardi [18] have demonstrated in vitro that magnesium ion will increase the mitochondrial uptake of calcium at a lower concentration gradient than without magnesium, which may also be a protective mechanism against higher intracellular concentrations of calcium.

Geffin and associates [3] have recently shown that the addition of increasing amounts of calcium in a cardioplegic solution increases the diastolic pressure development during infusion of cardioplegic solution as measured by a left ventricular isovolumic balloon. Magnesium decreased the development of left ventricular pressure during infusion and prevented the calcium-induced pressure increases and decrease of postischemic ventricular function. Thus, magnesium relaxed the contractive apparatus in the presence of a solution containing a high concentration of calcium, which allows sparing of ATP during induction of ischemic arrest and results in a gradual return of function on reperfusion.

The ability of magnesium to act as a myocardial protective agent in an isolated rat heart preparation is clear; however, before extrapolating the data to higher animals the particular species-specific Mg^{2+}/Ca^{2+} interactions must be taken into account. The amount of magnesium needed to reduce the peak developed tension of isolated myocardial preparations (by one half at 35°C) is 5 mmol/L in the rat, 18 mmol/L in humans, and 30 mmol/L in rabbits [19]. Magnesium does have an effect on ventricular function in an acceptable concentration range in humans. At least 15 mmol/L of Mg^{2+} (probably much more) is required to provide maximal postischemic ventricular performance and should be considered an essential ingredient in any crystalloid cardioplegia solution along with a calcium concentration of less than 0.05 mmol/L.

We would like to thank Gerald D. Kelly for his assistance in the isolated heart laboratory, and David M. Flynn for performing the ATP and total soluble protein determinations.

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DISCUSSION

DR TIMOTHY J. GARDNER (Baltimore, MD): This was a very nice presentation of an excellent study. There clearly is truth in the message that both calcium and magnesium may be important components of a cardioplegic solution, especially in the situation where a large volume of cardioplegic solution is administered. There may be a problem, however, in the way in which this study was carried out. To use the isolated perfused heart model, a model that we have used in our own laboratory for many years and a model that has been used productively by so many others, unfortunately introduces many departures from what is physiologically relevant.

In the present study, I believe that the message is correct that the ischemic heart is highly susceptible to alterations in the calcium content of the perfusate and possibly the magnesium content as well. Where this problem is especially important clinically is in the setting of postischemic reperfusion, much more so than in the situation of intermittent cardioplegic administration. This study confirms, at least by inference, what has been demonstrated in many other studies, namely, that the calcium content of the postischemic reperfusate is very important in the recovery process of the myocardium. In the clinical situation, no matter how much crystalloid cardioplegia you might use during the ischemic interval, there is some calcium and probably magnesium exposure of the heart from so-called noncoronary collateral blood flow. Because of this, the precise regulation of calcium and magnesium concentrations in the cardioplegic solution itself may be relatively less important.

The other important point of your presentation is to emphasize the fact that we do not know much about magnesium and its importance regarding cellular homeostasis and myocardial cell function. In addition, we know relatively little about the relationship between magnesium and calcium in the postischemic heart. But once again, I believe that the issues of major importance raised by this study will be in the setting of postischemic reperfusion. We need to know what ionic alterations, if any, in the content of the myocardial reperfusate will enhance functional recovery, and these types of studies will best be done using blood-perfused cardiac models.

DR BROWN: I agree with your comments and also believe that a main issue in myocardial protection lies in altering the reperfusate as well as in refining the cardioplegia solutions that are in use today.

Notice From the Southern Thoracic Surgical Association

The Thirty-eighth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Hyatt Regency Grand Cypress, Orlando, Florida, November 7–9, 1991. There will be a $250 registration fee for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 7, 1991. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1991, to Frederick L. Grover, MD, Program Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract submission form. These forms may be obtained from the Association's office or in this issue of *The Annals of Thoracic Surgery*. All slides used during the presentation must be 35 mm. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1991 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1991, and forwarded to F. Hammond Cole, Jr, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267.

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Bronchoalveolar Carcinoma: Factors Affecting Survival

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One hundred thirty-four consecutive patients (65 men and 69 women) underwent pulmonary resection for bronchoalveolar carcinoma. Mean age was 65 years. Lobectomy was done in 100 patients, pneumonectomy in 10, segmentectomy in 5, and wedge excision in 19. Only 10 patients had lymph node metastases (7.5%). The neoplasm was solitary in 111 patients (82.8%); 97 were in stage I, 4 were in stage II, 9 were in stage IIIa, and 1 was in stage IIIb. There were two operative deaths (1.5%). Thirty-nine complications occurred in 31 patients. Median follow-up was 5.1 years. Recurrent bronchoalveolar carcinoma developed in 45 patients. Five- and 10-year survival for patients in stage I was 75.2% and 62.0%, respectively. Survival for patients with T1 N0 M0 neoplasms was identical to expected survival and was 90.5% at 5 years, as compared with 55.4% for patients with T2 N0 M0 disease, only 35.9% for patients with multiple bilateral disease, and 0.0% for patients with bilateral disease ($p < 0.0001$). Other significant factors adversely affecting survival included the presence of signs and symptoms, diffuse malignant invasion, mucin-producing tumors, and the histological absence of scar. We conclude that bronchoalveolar carcinoma has a unique natural history that is more influenced by local neoplastic processes than by lymph node metastases. Early aggressive pulmonary resection is safe and offers the potential for cure. The presence of bilateral cancer, however, is ominous.

(Ann Thorac Surg 1991;51:368–77)

First described in 1876 [1], bronchoalveolar carcinoma (BAC) continues to remain controversial. The numerous names given to this neoplasm over the years (alveolar cell carcinoma, bronchiolar carcinoma, and bronchoalveolar carcinoma) attest to the uncertainties of histogenesis. Although most pathologists today support the existence of BAC as a separate and distinct lung cancer, questions frequently arise as to whether this neoplasm truly differs from conventional pulmonary adenocarcinoma, especially because overlap between features of these two carcinomas does occur and both cancers can coexist in the same patient. Controversy also exists as to the various clinical and pathological findings and as to how these relate to prognosis. Because of this continuing controversy, we have retrospectively reviewed our recent experience with this neoplasm.

Material and Methods

Between January 1, 1976, and December 31, 1983, a total of 4,080 consecutive patients with primary lung cancer underwent pulmonary resection at the Mayo Clinic; 1,492 (36.6%) had adenocarcinoma and 140 (3.4%) had bronchoalveolar carcinoma. Six of the 140 patients with BAC were excluded from further analysis because they were first seen with recurrent disease after having had a previous BAC resected elsewhere. The records of the remaining 134 patients were reviewed for presenting signs and symptoms, type of pulmonary resection performed, operative findings, complications, and long-term survival.

All chest roentgenograms were reviewed to determine presenting characteristics of BAC. All pulmonary lesions were classified according to the "Glossary of Terms for Thoracic Radiology" as recommended by the Nomenclature Committee of the Fleischner Society [2]. When multiple lesions were present, the largest was used to describe the findings on chest roentgenogram. A pulmonary mass was defined as any distinct lesion 3 cm or greater in diameter. A solitary pulmonary nodule was a well-demarcated lesion less than 3 cm in diameter completely surrounded by pulmonary parenchyma. The lesion was considered an infiltrate if it was a poorly delineated opacity without defined borders that neither destroyed nor displaced gross morphology. Lobar pneumonitis was a diffuse infiltrate involving a minimum of one lobe, often with the presence of an air bronchogram and little or no loss of volume. Each specific lesion was also evaluated for associated cavitation and atelectasis.

The microscopic findings of all pathological specimens were reviewed by two of us (M.S.H., T.V.C.). All histo-

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logical assessments were based solely on hematoxylin and eosin stains. Lung carcinomas were accepted as BAC if the neoplasm was an adenocarcinoma that demonstrated a growth pattern along preexisting lung architecture without invasive or destructive growth. Many BACs were associated with localized scarring, and, in such cases, the distinction of stromal invasion from growth along the distorted architectural framework of the scar was arbitrary. In general, the presence of jagged tumor cell nests and a fibroblastic stromal reaction around the cells was considered indicative of stromal invasion. Histologically, each specimen was evaluated for the type of tumor cell (mucinous or nonmucinous) and the presence of localized scarring associated with the tumor. Mucinous cells were defined as those with basally located nuclei and eosinophilic to grayish cytoplasm typical of mucin-producing cells. The following features were also individually assessed: nuclear vacuoles, zones of solid growth within air spaces, papillary growth, clear cell change, necrosis, psammoma bodies, interstitial lymphoid reaction, and interstitial fibrous thickening. The degree of cellular differentiation was graded by Broders' pathological classification [3].

All solitary neoplasms were postsurgically staged according to the current International TNM Classification System for Lung Cancer [4]; however, if multiple lesions were present, patients were not classified but simply separated into those with unilateral and bilateral disease. Complete lymph node sampling was done in all patients who had curative resection. This included high and low ipsilateral paratracheal, subcarinal, and inferior pulmonary ligament lymph nodes. Any other suspicious lymph nodes were also sampled. Lobar lymph nodes were analyzed in the resected specimens. Operative mortality included all deaths occurring within 30 days of operation and all deaths occurring beyond 30 days but during the same hospitalization. Respiratory failure was defined as mechanical ventilation required for longer than 72 hours, and air leaks were defined as prolonged if they lasted for more than 7 days.

In this report, a pulmonary resection was considered curative if all known BAC was removed at the time of initial operation. Recurrent BAC was defined by criteria previously published by us for recurrent lung cancer [5, 6]. Survival probabilities were estimated by the Kaplan-Meier actuarial method [7] using the date of initial operation as the starting date. The Lung Cancer Study Group has recently reported that death is not a suitable therapeutic end-point for the evaluation of lung cancer treatment, as many deaths occur from causes other than lung cancer [8]. Consequently, we have elected to report some of our survival data using death from BAC as the end-point. However, when comparison of patient survival to expected survival was analyzed, death from *all* causes was the end-point. Expected survival curves were based on deaths from all causes from west-north central United States 1980 life-table data and were matched for age and sex. The influence of different variables on survival was analyzed with the log-rank test for discrete variables [9] and with the proportional hazards model of Cox for continuous variables [10]. Multivariate analysis was used to evaluate all significant univariate relationships using both backward elimination and forward selection processes. Comparison of recurrent BAC and cell types between groups was done with Fisher's exact test.

Table 1. Preoperative Symptoms

Symptom	No. of Patients
Cough	30
Sputum production	23
Chest pain	14
Hemoptysis	6
Weight loss	6
Shortness of breath	5
Fatigue	4
Fever	4
Wheezing	2
Osteoarthropathy	1
Herpes zoster	1

Clinical Findings

There were 65 male and 69 female patients. Age ranged from 26 to 83 years (median, 65 years). Ninety-one patients (67.9%) were asymptomatic. Cough was present in 30 of 43 symptomatic patients (69.8%). Sputum production and pain were the next most common symptoms (Table 1). Presenting chest roentgenograms demonstrated a single lung lesion in 121 patients (90.3%). Most were seen as an irregular pulmonary mass greater than 3 cm in diameter (78 patients, 58.2%). A solitary pulmonary nod-

Table 2. Preoperative Chest Roentgenographic Findings

Finding	No. of Patients	Percent
Number		
Single	121	90.3
Multiple	13	9.7
Location		
Peripheral	132	98.5
Central	2	1.5
Description		
Pulmonary mass >3 cm	78	58.2
Solitary pulmonary nodule ≤3 cm	15	11.2
Infiltrate	11	8.2
Lobar pneumonitis	30	22.4
Associated findings		
Cavitation	19	14.2
Atelectasis	7	5.2
Diameter		
≤3 cm	89	66.4
>3 cm	45	33.6

Table 3. Other Preoperative Examinations

Examination	No. of Patients	Additional Information
Sputum cytology	91	16
Bronchoscopy	75	32
With TBLB	49	25
Without TBLB	26	7
Tomograms	74	17
Computed tomography	26	12
Transthoracic needle aspiration	4	2

TBLB = transbronchoscopic lung biopsy.

Table 5. Location of Neoplasms

Location	No. of Patients	Percent
Right upper lobe	28	20.9
Right middle lobe	8	6.0
Right lower lobe	21	15.7
Left upper lobe	37	27.6
Left lower lobe	17	12.7
Multiple unilateral	14	10.4
Multiple bilateral	9	6.7

ule was uncommon, occurring in only 15 patients (11.2%). Roentgenographic evidence of disease was bilateral in 9 of the 13 patients with multiple lesions (Table 2). In addition to routine chest roentgenograms, sputum cytology, tomograms, and bronchoscopy were the most frequently performed diagnostic tests (Table 3). These tests were considered to have provided additional diagnostic information if they demonstrated additional lesions, evidence of chest wall or mediastinal invasion, lymph node enlargement, or the identification of carcinoma cells. Overall, the diagnosis of carcinoma was made preoperatively in 41 patients (30.6%).

Mediastinoscopy was used selectively and was performed in only 15 patients (11.2%); all results were negative. Indication for mediastinoscopy was advanced disease in 11 patients, high risk in 3, and diagnostic in 1. Seven of the 9 patients with bilateral lesions underwent thoracotomy for diagnosis only, 1 had staged bilateral thoracotomies, and 1 had a median sternotomy. Lobectomy was the most frequently performed procedure (70.1%). Wedge excisions were done in 19 patients; only 8, however, had all known cancer removed by this procedure (Table 4). The resection was considered curative in 122 patients (91.0%).

Sixty-two patients (46.3%) had tumors involving the right lung, 63 (47.0%) had the left lung involved, and 9 (6.7%) had bilateral lesions (Table 5). At the time of operation, BAC was solitary in 111 patients (82.8%) and multiple in 23 (17.2%). Solitary neoplasms were most commonly located in the upper lobes (58.6%). Eight of the patients with multiple lesions had lesions that numbered greater than ten and all underwent noncurative operations. Synchronous lesions in the remaining 15 patients ranged from two to five (median, two). The distribution by TNM classification is shown in Table 6. Only 10 patients had evidence of lymph node metastases (7.5%); 2 patients had N1 disease and 8 had N2. Seventeen of the 23 patients with multiple lesions had no evidence of lymph node metastases; in the remaining 6, lymph node status was unknown because thoracotomy was performed for biopsy only. The parietal pleura was invaded in 6 patients; 3 had T3 lesions, 1 had T4, and 2 had multiple lesions.

Tumor diameter ranged from 3 mm to involvement of an entire lung (median, 2.3 cm). The 30 patients with lobular pneumonitis on presenting chest roentgenogram all had a diffuse infiltrate that involved a minimum of one lobe. At gross examination the involved lobe(s) was consolidated with loss of normal architecture. Histologically, all areas of consolidation were BAC. Twenty of these 30 patients had postsurgical stage I disease (T2 N0

Table 4. Operative Procedure

Procedure	No. of Patients	Curative Resection
Pneumonectomy	10	10
Lobectomy	94	93
Bilobectomy	6	6
Segmentectomy	5	5
Wedge	18	7
Sternotomy and bilateral wedge	1	1
Total	134	122 (91.0%)

Table 6. TNM Classification

Classification	Number	Noncurative Resection	Operative Death
Stage I			
T1 N0 M0	58	0	0
T2 N0 M0	39	0	1
Stage II			
T1 N1 M0	2	0	0
T2 N2 M0	2	0	0
Stage IIIa			
T3 N0 M0	3	1	0
T1 N2 M0	3	1	0
T2 N2 M0	3	0	0
Stage IIIb			
T4 N0 M0	1	1	0
Multiple lesions[a]			
Unilateral	14	2	1
Bilateral	9	7	0

[a] All sampled lymph nodes were negative for tumor.

Table 7. Histological Features of Bronchoalveolar Carcinoma

Feature	No. Present
Cell type	
Nonmucinous	60
Mucinous	55
Mixed	19
Interstitial findings	
Thickening	89
Scar	72
Lymphoid reaction	58
Cellular findings	
Papillae	122
Nuclear vacuoles	75
Solid foci	44
Necrosis	12
Clear cell	6
Gross findings	
Diffuse malignant invasion	30

M0); the remaining 10 had multiple tumors. The histological features of all neoplasms are listed in Table 7. Mucinous cell type was more common in the 30 patients with diffuse malignant invasion (66.7%) than in the remaining 104 patients (36.6%; $p < 0.01$). The neoplasm was grade 1 in 55 patients, grade 2 in 72, grade 3 in 6, and grade 4 in 1.

Results

Hospitalization ranged from 4 to 20 days (median, 7 days). Thirty-nine complications (Table 8) occurred in 31 patients (23.1%). There were two operative deaths (mortality, 1.5%). Cause of death was myocardial infarction at 3 days and respiratory failure from adult respiratory distress syndrome at 4 days. Both deaths occurred in patients who had curative resection.

Follow-up was complete in 128 of the 132 operative survivors (97.0%) and ranged from 0.5 to 12.8 years (median, 5.1 years). All patients who are currently known to be alive were followed up for at least 5 years (range, 5.0 to 12.8 years; median, 8.1 years). Four patients had incomplete follow-up; when last evaluated, however, all 4 were still alive and free of BAC, 2 patients at 3 years and 2 at 4 years.

Table 8. Postoperative Complications

Complication	No. of Patients
Prolonged air leak	16
Dysrhythmia	9
Atelectasis	8
Respiratory failure	3
Pulmonary embolus	1
Vocal cord paralysis	1
Myocardial infarction	1

Table 9. Location of Recurrent Bronchoalveolar Carcinoma

Location	No. of Patients
Contralateral lung	14
Ipsilateral lung	12
Bilateral lung	10
Distant	7
Mediastinal lymph nodes	1
Unknown	1

Recurrent cancer developed in 45 of the 120 operative survivors who had curative pulmonary resections (37.5%); all recurrences were histologically BAC. New pulmonary lesions (80.0%) were the most common type of recurrence (Table 9) and most were seen as solitary lesions. Time to recurrence ranged from 7 to 73 months with a median of 30 months. Recurrent BAC developed in 10 patients with T1 N0 M0 disease (17.2%), as compared with 18 with T2 N0 M0 (47.4%) ($p < 0.05$). Bronchoalveolar carcinoma also recurred in 3 patients with stage II disease (75.0%), in 5 with stage IIIa (71.4%), and in 12 with multiple neoplasms (unilateral, 90.3%; bilateral, 100.0%). The rate of recurrence in patients with multicentric disease was significantly greater than in patients with T1 N0 M0 disease ($p < 0.01$). Thirty patients with recurrent BAC received chemotherapy, 19 received radiation therapy, and 19 underwent further pulmonary resection, 14 of which were thought to be curative.

Overall, 76 patients are known to have died (Table 10). Twelve of these patients had noncurative pulmonary resections and all died of persistent cancer; median survival for these 12 patients was 34 months and ranged from 2 to 46 months. Two other deaths were operative deaths following pulmonary resection. The remaining 62 deaths occurred in the 120 operative survivors who had curative pulmonary resection. Cause of death was recurrent BAC in 44, cardiac in 6, breast cancer in 3, liver failure in 2, renal failure in 1, prostate cancer in 1, colon cancer in 1, trauma in 1, pulmonary embolism in 1, and unknown in

Table 10. Status at Follow-up

Status	All Patients	Patients With Recurrence
Alive, no disease	57	2[a]
Alive, with disease	1	1
Dead, due to BAC	56[b]	41
Dead, other cause	18	1
Dead, unknown cause	2	0

[a] Recurrence developed and was successfully resected with second operation. [b] Includes 12 patients who had noncurative resections.

BAC = bronchoalveolar carcinoma.

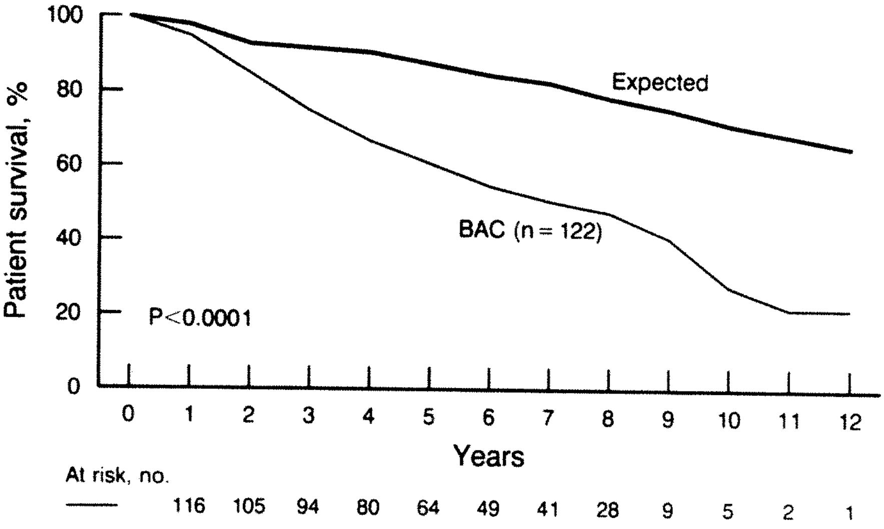

Fig 1. Overall probability of survival (death from any cause) of 122 patients undergoing curative pulmonary resection for bronchoalveolar carcinoma. Expected survival represents survival of a group of patients matched for age and sex. Zero time on abscissa represents the date of pulmonary resection.

2. In all 5 patients who died from other types of cancer, the specific extrapulmonary primary site was histologically documented as the cause of death in each patient.

At last follow-up, 58 patients were alive, only 1 with BAC. Three of the 14 patients who had a second curative pulmonary resection are alive, 2 without disease at 1 and 6 years after the second operation and 1 with BAC at 7 years; the remaining 11 have all died of recurrent BAC.

Overall, the estimated 5- and 10-year survival (death from all causes) for all 122 patients undergoing curative resection was 60.8% and 28.1%, respectively (Fig 1). When only deaths from BAC were considered, 5- and 10-year survival was 65.4% and 50.4%, respectively (Fig 2). Five- and 10-year survival (death from BAC) for patients with stage I disease was 75.2% and 62.0%, respectively (Fig 3); 5-year survival for patients with T1 N0 M0 tumors was 90.5%, as compared with only 55.4% for patients with T2 N0 M0 neoplasms ($p < 0.0001$). Survival (death from all causes) for patients with T1 N0 M0 neoplasms did not differ significantly from expected survival of patients matched for age and sex (Fig 4). Survival of patients with multiple tumors is shown in Figure 5. Five-year survival (death from BAC) for patients with unilateral and bilateral disease was 35.9% and 0.0%, respectively ($p < 0.001$).

Preoperative factors that were found to significantly affect survival to death from BAC for all patients are listed in Table 11. Chest roentgenographic findings suggesting multiple lesions or lobar pneumonitis (large diffuse infiltrates) were poor prognostic signs. Similarly, the preoperative diagnosis of carcinoma, either by bronchoscopy or sputum cytology, and the presence of symptoms were significantly associated with decreased survival. A history of cigarette smoking did not affect survival.

The only operative factor that affected survival was whether a curative pulmonary resection had been performed. Among those patients who had a curative resection, median survival was 7.2 years, as compared with only 1.7 years for those who did not ($p < 0.001$). The extent of pulmonary resection did not influence survival. There were 8 patients who had curative wedge excisions; 6 are still alive from 5.2 to 7.1 years after excision (median,

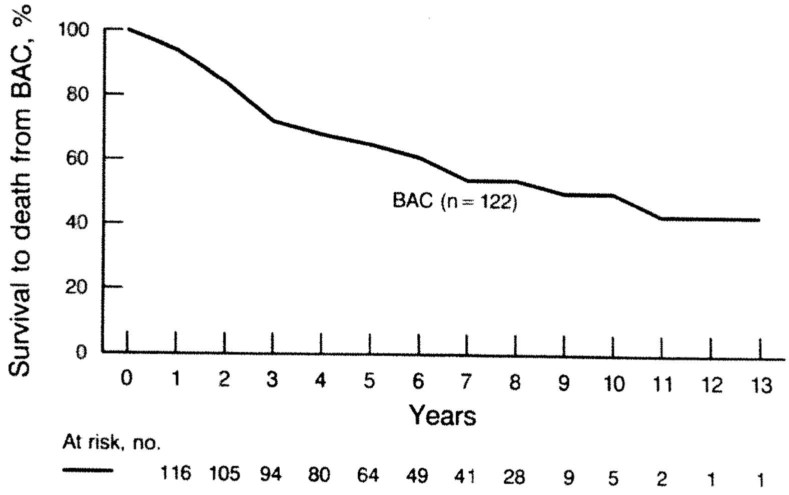

Fig 2. Probability of survival (death from bronchoalveolar carcinioma [BAC]) of 122 patients undergoing curative pulmonary resection. Zero time on abscissa represents the date of pulmonary resection.

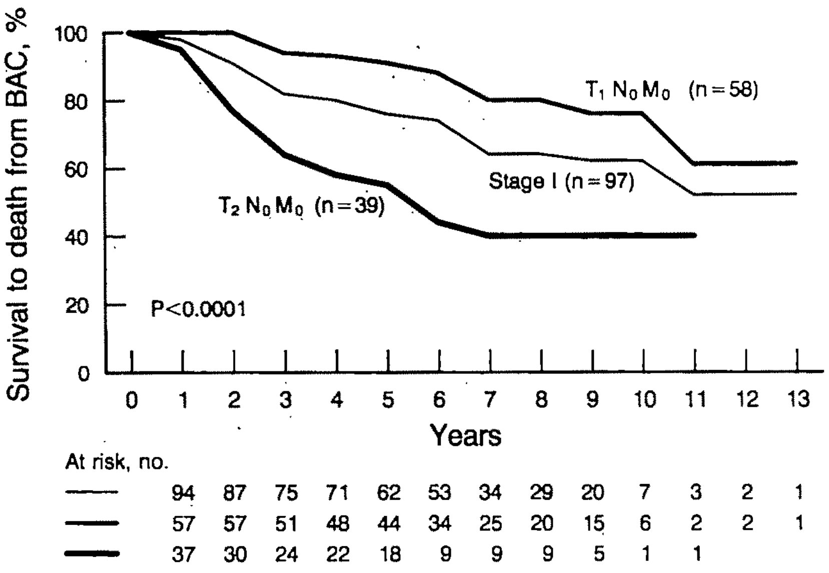

Fig 3. Probability of survival (death from bronchoalveolar carcinoma [BAC]) of 97 patients with postsurgical stage I neoplasm by TNM classification undergoing pulmonary resection. Zero time on abscissa represents the date of pulmonary resection.

5.8 years). The remaining 2 patients both died of BAC at 4 years.

Pathological features that affected survival are shown in Table 12. The presence of multiple tumors, diffuse malignant invasion, and mucin-producing tumors were ominous findings. In contrast, the finding of dense collagen (scar) within the tumor was associated with a favorable outcome. Median survival for those patients with scar was greater than 13.5 years, as compared with only 3.6 years if scar was absent ($p < 0.001$).

Because patients with stage II and stage III disease and patients with multiple lesions had a reduced long-term survival, we analyzed separately factors affecting survival in patients with stage I disease. Significant risk factors identified were nearly identical to factors affecting all patients. The presence of chest symptoms ($p < 0.0001$), positive sputum cytology ($p < 0.001$), absence of associated scar ($p < 0.01$), and the presence of diffuse malignant invasion ($p < 0.0001$) all adversely affected survival. Mucin production, however, had no significant effect in stage I patients.

All risk factors identified in the 134 patients by univariate analysis were also evaluated by multivariate analysis; factors found to significantly affect survival to death caused by BAC with this latter analysis were the presence of chest symptoms and T2 N0 M0 neoplasms. Most of the other previously mentioned univariate risk factors were also identified as independent predictors of survival. However, multivariate analysis of observed data in this series has to be interpreted with care. Significant factors present in cohorts with small numbers of patients may not be interpreted reliably. Furthermore, potentially significant factors may be difficult, if not impossible, to identify because the number of observed events in many subgroups was initially small and became smaller during the stepwise regression process of the hazards model. Con-

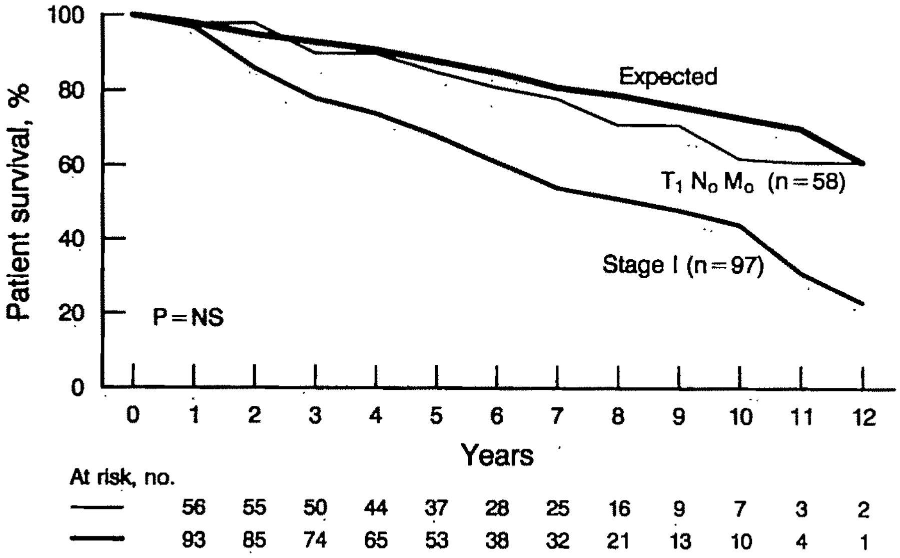

Fig 4. Overall probability of survival (death from any cause) of 97 patients with postsurgical stage I neoplasm by TNM classification undergoing curative pulmonary resection. Expected survival represents survival of a group of patients matched for age and sex. Zero time on abscissa represents the date of pulmonary resection.

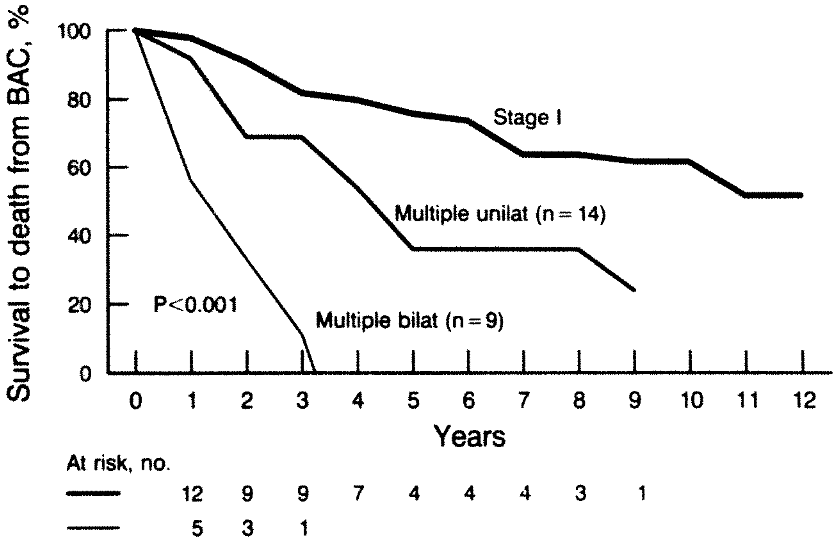

Fig 5. Probability of survival (death from bronchoalveolar carcinoma [BAC]) of 97 patients with postsurgical stage I neoplasm undergoing pulmonary resection, as compared with 23 patients with multiple neoplasms undergoing pulmonary resection. Zero time on abscissa represents the date of pulmonary resection.

sequently, the results of the multivariate analysis do not necessarily exclude the significance of the univariate analysis.

Comment

Bronchoalveolar carcinoma continues to be the least common type of bronchogenic carcinoma, occurring in only 3.4% of our patients undergoing pulmonary resection for lung cancer during an 8-year period. This is in accordance with the literature, in which the prevalence has been reported to vary from 1% to 9% [11–14]. Women accounted for 51.5% of these patients in our study, which is slightly higher than the literature mean of approximately 40% previously reported [11–14]. Also, the median age of our patients was 65 years, which was higher than that previously reported [11–14]. These demographic findings, however, may reflect the tertiary nature of our practice rather than a change in incidence.

Table 11. Preoperative Factors Affecting Survival to Death Caused By Bronchoalveolar Carcinoma

Factor	No. of Patients	Median Survival (y)	*p* Value
Number of lesions			
1	121	10.0	<0.002
>1	13	2.5	
Size			
≤3 cm	89	8.5	<0.001
>3 cm	45	2.9	
Lobar pneumonitis			
No	104	10.5	<0.0001
Yes	30	2.5	
Cytology			
Negative	75	9.5	<0.0001
Positive	16	2.0	
Symptoms			
Absent	91	>13.5	<0.0001
Present	43	2.5	

We continue to believe that BAC is a unique and distinct pathological entity that is different from pulmonary adenocarcinoma. Although overlap between the

Table 12. Pathological Features Affecting Survival to Death Caused by Bronchoalveolar Carcinoma

Feature	No. of Patients	Median Survival (y)	*p* Value
Stage			
I	97	>13.5	<0.05[a]
II	4	(<9.0)[b]	
IIIa	9	2.9	
IIIb	1	(2.7)[b]	
Multiple unilateral	14	4.9	<0.0001[c]
Multiple bilateral	9	1.9	<0.0001[c]
TNM Classification			
T1 N0 M0	57	>13.5	<0.0001
T2 N0 M0	40	5.0	
Gross pathology			
Diffuse malignant invasion			
No	104	>13.5	<0.0001
Yes	30	3.0	
Histology			
Nonmucinous[d]	60	10.5	<0.02
Mucinous[d]	55	5.0	
Scar			
Yes	72	>13.5	<0.001
No	62	3.6	

[a] Compares stage I with stage IIIa. [b] Patient numbers are too small to obtain meaningful statistics. [c] Compares stage I with multiple tumors. [d] Mixed features were present in an additional 19 patients.

histological features of BAC and pulmonary adenocarcinoma is common, BAC consistently demonstrates a growth pattern along preexisting lung architecture without invasive or destructive growth. The association of BAC with scarring has been recognized for many years, but whether the neoplasm actually produces collagen or just develops in an old scar is uncertain. Our study added little to this controversy other than to document that scar was present.

Roentgenographically, BAC was seen in several different patterns. Most commonly, the neoplasm is seen as a single mass greater than 3 cm in diameter; however, the finding of a "solitary pulmonary nodule" is unusual and occurred in only 11.2% of our patients. The initial clinical picture may also be that of unresolving pneumonia, and many of our patients had roentgenographic changes present for a prolonged period of time before surgical intervention was considered. Finally, the neoplasm may be multicentric. Cavitation and atelectasis are unlikely to be present in any form of presentation.

Our data suggest that the natural history of BAC is different from other types of bronchogenic carcinoma in that survival is, in general, prolonged and more influenced by the extent of lung involvement than by the extent of lymph node metastases. Bronchoalveolar carcinoma tends to be seen as localized stage I disease, as was the situation in nearly 75% of our patients. Moreover, lymph node metastases were uncommon, occurring overall in only 7.5% of our patients. These findings are reflected in an excellent survival. Five-year survival for *all* patients having a curative resection was 65.4%. This is better than that observed with any of the other types of lung cancer [13]. Moreover, when only patients with T1 N0 M0 neoplasms were considered, survival did not differ significantly from expected survival, suggesting that patients with this TNM subset were cured.

Is BAC multicentric in origin? Many reports over the years have questioned this concept [12, 15, 16]. Our data suggest that BAC has a unicentric origin. In our series, BAC was multiple in only 17.2% of patients. When multicentric disease was present, it was associated with a poorer prognosis, even if the tumors were small and completely resected. In contrast, if resection was accomplished when solitary tumors were small, survival was identical to expected survival, indicating that recurrence, including a new primary BAC, was unlikely. Consequently, multiple lesions may represent advanced disease rather than multicentric origins with progression occurring by direct extension along the bronchial tree or by aerosolization of tumor emboli. This concept may be further supported by the better survival observed in patients with multiple unilateral disease than in those with bilateral lesions, implying that unilateral lesions may more likely represent extensive local disease, whereas bilateral lesions may more likely represent aerosolized metastatic disease.

Two histopathological types of BAC have been recognized, both of which influence long-term survival [15, 16]. Our data support this concept. Microscopic mucin production characterized one cell type and was associated with a worse prognosis; most occurred in patients with diffuse malignant invasion. The second cell type was characterized as nonmucinous and was associated with a better survival; most were T1 neoplasms. Several other pathological characteristics of BAC are also important. Multiple lesions and diffuse malignant invasion were ominous findings. In contrast, the presence of associated scar was a favorable finding. How any of the above factors affected patients who had lymph node metastases could not be ascertained because of the low incidence of lymph node involvement. Thus, long-term survival of patients with BAC in our study was determined more by the local characteristics of the neoplasm than by distant spread.

This information may be helpful in predicting prognosis beyond that obtained from postsurgical stage. Stage I disease was present in the majority of our patients undergoing pulmonary resection, and potentially curative resection was possible in all; yet these risk factors clearly had considerable influence on survival. The number of patients in other stages, however, was too small to allow a similar meaningful analysis.

Patients with multiple tumors have a poor prognosis. Five-year survival for unilateral and bilateral disease was 35.9% and 0.0%, respectively. The adverse effect of synchronous lung cancers has been previously documented by us [17] and others [18]. Our study supports the conclusion of Deslauriers and associates [18] that synchronous lesions have a biology similar to that of resectable stage III disease, and we agree that these patients, including those with multiple BAC, should be classified in the TNM system as having stage IIIa rather than multiple stage I.

The evaluation and management of BAC is similar to that of other types of lung cancer. Computed tomography, however, is of more value in detecting multicentric disease than mediastinal adenopathy, and *routine* mediastinoscopy is not indicated because of the low incidence of lymph node metastases. If bilateral disease is suspected preoperatively, documentation of the extent of disease is necessary, but pulmonary resection is not indicated, as none of our patients were long-term survivors. Patients with unilateral disease should undergo pulmonary resection if otherwise in good health, including those with multiple unilateral disease, because 36% of these latter patients were still alive at 5 years after curative resection. At operation, complete lymph node assessment is mandatory. After curative resection, patients should be evaluated every 4 to 6 months for the first 2 years and annually thereafter [5, 6]. Evaluation should include physical examination, chest roentgenogram, sputum cytology, and blood chemistry. If pulmonary BAC recurs, further pulmonary resection should be considered, although long-term survival seems unlikely.

We conclude that BAC has a unique natural history that is more influenced by local neoplastic processes than by lymph node metastases. Early aggressive pulmonary resection is safe and offers the potential for cure. If multiple unilateral disease is present, strong consideration should also be given to pulmonary resection. The presence of multiple bilateral cancer, however, is ominous.

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DISCUSSION

DR ERIC L. CEITHAML (Jacksonville, FL): I notice that some of the recent literature is now showing that there appears to be reduced long-term survival in patients with lung cancer greater than 2 cm. Your cut-off was 3 cm. Have you reviewed your survival statistics with respect to smaller tumors?

DR DALY: On the basis of the accepted lung cancer staging system, we considered T1 tumors to be those less than or equal to 3 cm in diameter. We did not evaluate tumor diameter as a continuous variable. We found that patients with T1 lesions did very well; in fact, these patients had an estimated survival similar to expected survival. In contrast, patients with larger lesions, particularly those that involved a lobe, did poorly.

DR LEWIS WETSTEIN (Freehold, NJ): I commend you on your results.

We continue to be challenged by our patient population with dismal borderline pulmonary function who require a lung resection. Therefore, we routinely attempt limited lung resection, ie, wedge or segmentectomy, for T1 N0 M0 lesions. We were delighted to be able to report that our results were superimposable comparing wedge or segmentectomy versus lobectomy for these limited lesions [1].

Could you dissect out your data and tell us what your results would be for cure for limited resections versus the lobectomy?

DR DALY: The 5 patients who underwent segmentectomy did as well as the patients who had lobectomy. Eight patients had curative wedge excisions; at follow-up, however, recurrent disease developed in 2 patients and both died of bronchoalveolar carcinoma. The remaining 6 patients were followed up for a minimum of 5 years and all are alive without disease.

DR KAMAL A. MANSOUR (Atlanta, GA): I thought bronchoalveolar carcinoma is divided into two types—a localized form, which is resectable, and a diffuse perivascular form, which is inoperable. Is your classification a new one? Is it solitary versus diffuse and unilateral versus bilateral?

The second question is, what do you do for diffuse bilateral disease?

DR DALY: In terms of classifying bronchoalveolar carcinoma, there indeed are two groups. One group is more likely to consist of mucinous cells and tends to be seen in a diffuse manner involving large portions of lung. These patients have an ominous prognosis. The second group has a nonmucinous cell type and is seen in a more localized manner. The majority of these latter patients have resectable disease, and nearly all have an excellent prognosis.

Patients with diffuse bilateral disease did poorly, and all were dead at 3 years. Consequently, we believe that patients with bilateral disease should have operation for diagnosis only.

DR C. GREGORY LOCKHART (Richmond, VA): I noticed in your long-term follow-up that there was a substantial incidence of recurrence between 5 and 12 years. I was interested in those patients who had recurrence after 5 years: where was the recurrence? Was the recurrence local disease or distant metastasis, and what were the factors that influenced recurrence?

DR DALY: Recurrence developed in 38% of our patients during follow-up. All of our living patients were followed up for more than 5 years. Although the majority of recurrences were within 5 years, patients tended to live for an extended period of time after recurrence. Thus, the natural history of bronchoalveolar carcinoma is different from that of other types of lung cancers in that growth is slower. Nonetheless, recurrence remains an ominous sign. Only 2 patients with recurrence were alive without disease at follow-up. Most recurrences were in the lung: either ipsilateral, bilateral, or both.

DR J. B. ZWISCHENBERGER (Galveston, TX): I appreciate the fact that you use the new international lung cancer staging system, but I would like you to describe exactly how you did your mapping and how you sampled lymph nodes intraoperatively to determine the staging.

DR DALY: Complete lymph node sampling was done in all patients who had curative resection. This included high and low paratracheal, subcarinal, and inferior pulmonary ligament lymph nodes. Any other suspicious lymph nodes were also sampled. In addition, lobar lymph nodes were analyzed in the resected specimen. If wedge excisions were done, appropriate lobar lymph nodes were sampled. Staging then was determined by the size of the primary tumor and location of lymph nodes.

DR ZWISCHENBERGER: So every patient was routinely completely mapped.

DR DALY: Routinely and completely mapped.

DR FREDERICK L. GROVER (San Antonio, TX): I had the opportunity a few years ago to review the Lung Cancer Study Group experience of 235 patients who underwent resection for bronchoalveolar carcinoma. Our study also demonstrated a very high preponderance of T1 N0 disease, which did quite well, as opposed to more advanced disease, which did very poorly. One question that we could not answer in that study, because of the multicenter aspect of it, was what percentage of patients with bronchoalveolar carcinoma are operated on and what percentage never come to operation. Can your Mayo Clinic study shed some light on this?

DR DALY: There were approximately 8,000 patients with lung cancer evaluated at the Mayo Clinic during the time period represented in this review. Pulmonary resection was performed in 4,080 patients. If we can extrapolate this observation to bronchoalveolar carcinoma, approximately half the patients will eventually come to operation.

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Primary Cysts and Tumors of the Mediastinum

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A retrospective analysis was performed on 230 patients with primary cysts and tumors of the mediastinum seen at our institution from January 1944 to April 1989. We divided these patients into two groups. Group 1 was seen before 1970 and group 2 was seen from January 1970 to April 1989. There was a significant increase in the prevalence of malignancy in group 2 (47.2% versus 17.1%; $p < 0.0001$) due to an increase in the number of lymphomas (22.6% versus 3.5%; $p < 0.001$) and malignant neurogenic tumors (6.8% versus 1.1%; $p = 0.0528$). There was a significant increase in the number of malignant tumors in the anterior (59.5% versus 30.9%; $p = 0.0022$) and paravertebral (28.5% versus 2.8%; $p = 0.0027$) compartments in group 2. More patients with these tumors were symptomatic in group 2 (63.6% versus 5%; $p = 0.0422$). There was an increase of ancillary diagnostic studies performed to evaluate these tumors (76.0% versus 34.5%; $p = 0.0422$). Logistic regression analysis identified date of presentation ($p < 0.005$), symptoms ($p < 0.01$), size ($p < 0.005$), and the anterior mediastinal compartment ($p < 0.005$) as preoperative predictors of malignancy. The surgical approach to these tumors included more median sternotomy (30.1% versus 10.7%; $p = 0.0008$), anterior mediastinotomy, and cervical mediastinoscopy in group 2 (1.1% versus 17.5%; $p = 0.0002$). Long-term results support surgical resection in benign lesions and an aggressive multimodality approach to malignant lesions.

(Ann Thorac Surg 1991;51:378–86)

Primary cysts and tumors of the mediastinum are being reported with increasing frequency. More than 2,400 such lesions have been reported in multiple large series [1–3]. The histological distribution, location, clinical presentation, diagnostic evaluation, and treatment of these tumors have been partially defined by these series. Recently, a large series from Duke University [1] has demonstrated changes in the histological and anatomical distribution of mediastinal tumors. This report is important; however, as noted in their discussion, these changes may in part reflect referral patterns to the Duke Medical Center.

Walter Reed Army Medical Center is a tertiary care center with a referral base that has not changed for the duration of this study [4]. We reviewed our series of patients with primary mediastinal cysts and tumors to evaluate changes in clinical presentation, diagnosis, and treatment over a 45-year period. We also analyzed our series for predictors of malignancy.

Material and Methods

All the records of the Thoracic Surgery Service at Walter Reed Army Medical Center were reviewed to identify patients with primary mediastinal cysts and tumors. Patients with metastatic disease of the mediastinum, direct extension of lung malignancies into the mediastinum, esophageal malignancies, cardiac tumors, infection, sarcoid, and hernias into the mediastinum were excluded. Patients with disseminated malignancy in whom a diagnosis was made by extrathoracic biopsy were also excluded. Patients in whom insufficient histological data were available to confirm the diagnosis were excluded. Information on the patients was obtained through Thoracic Surgery Clinic charts, in-patient records, pathology records, operation reports, Walter Reed Tumor Registry, and Hematology Oncology Clinic records.

Each chart was reviewed for demographic data, clinical presentation, and diagnostic investigation. The operative approach and procedure and the size, location, and histological diagnosis of the tumor or cyst were recorded. Postoperative morbidity and mortality were noted as well as long-term follow-up on the patients.

The patients were divided into two groups: group 1 included those patients seen before 1970. Group 2 included those patients seen from 1970 to April 1989. The two groups were compared to evaluate changes in these patients with time. Factors evaluated for change with time included histological diagnosis, clinical presentation, diagnostic evaluation, therapeutic approach, morbidity, and mortality. Statistical analysis was performed on all preoperative data recorded to determine predictors of malignancy.

For the purposes of our study, we divided the mediastinum into anterior, middle, and posterior mediastinum as described by Burkell and associates [5]. Chi square analysis was used to compare changes in the two groups with time. Yates' correction was used for groups less than

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30. Logistic regression analysis was used to define preoperative predictors of malignancy and their relationship to each other. Wilcoxon rank sum test was used to assess the overall validity of the logistic regression model. To account for the lack of tumor size data in 82 patients, the average size was used for these patients.

Results

There were 245 patients in our database. In 15 patients, there was insufficient histological material to categorize them and they were excluded from the study. Thus, there were 230 patients in the study with 84 patients in group 1 and 146 patients in group 2.

Demographic Data

There were 92 female and 138 male patients in the study. The mean age in the series was 28.8 ± 17.9 years with a range of newborn to 69 years. There were 185 white patients, 34 blacks, 4 Orientals, and 3 Latin patients. In 4 patients, this datum was not available. Fifty-four patients were younger than 18 years of age in our study. Comparing group 1 with group 2, there were no significant changes in the age or race distribution of the patients or number of pediatric patients. There was a significant increase in the number of female patients in group 2 ($p < 0.05$).

Tumor Histology

There were 84 malignant tumors and 146 benign tumors in the series. The distribution of histological diagnoses in this series is shown in Table 1. Thymic neoplasms were most common in the series. They represented 24.3% of the total group. The thymic neoplasms consisted of 17 malignant tumors and 39 benign tumors. Histologically, these included thymoma, thymic hyperplasia, thymic cyst, thymolipoma, squamous cell carcinoma of the thymus, and liposarcoma. We included these specific histological types together because all these tumors shared a close anatomical relation to the thymus and were tumors found within the substance of the thymus. Neurogenic tumors represented 16.9% of our total group. There were 28 benign tumors and 11 malignant tumors. The neurogenic tumors included ganglioneuroblastoma, neuroblastoma, neurilemoma, neurofibroma, and ganglioneuromas. All the patients with malignant neurogenic tumors were in the pediatric age group except for 1 who was 22 years of age.

Patients with lymphoma represented 15.7% of our group. The lymphomas were divided into Hodgkin's (9.6%) and non-Hodgkin's lymphoma (6.1%). There were 22 germ cell tumors in the series representing 9.5% of our population; 14 were benign and 8 were malignant. The tumors included 14 benign teratomas, 1 malignant teratoma, 3 seminomas, and 4 nonseminomatous germ cell tumors. There were 45 cystic lesions of the mediastinum representing 19.1% of the series. These cysts included pericardial cysts, bronchogenic cysts, enteric cysts, and 1 cyst of undetermined origin.

Comparing group 1 with group 2 (Fig 1), there was a

Table 1. Histologic Distribution of Primary Cysts and Tumors of the Mediastinum

Type	Benign	Malignant	Total
Thymic			
Thymoma	17	14	31
Thymic hyperplasia	6	0	6
Thymic cyst	11	0	11
Enlarged thymus	2	0	2
Squamous cell carcinoma of thymus	0	2	2
Ectopic normal thymus	1	0	1
Thymic lipoma	2	0	2
Sarcoma	0	1	1
Total thymic	39	17	56
Cyst			
Bronchogenic	24	0	24
Enteric	12	0	12
Pericardial	8	0	8
Undetermined origin	1	0	1
Total cyst	45	0	45
Neurogenic			
Ganglioneuroblastoma	0	6	6
Neuroblastoma	0	5	5
Ganglioneuroma	16	0	16
Neurilemoma	10	0	10
Neurofibroma	2	0	2
Total neurogenic	28	11	39
Lymphoma			
Hodgkin's	0	22	22
Non-Hodgkin's	0	14	14
Total lymphoma	0	36	36
Germ cell			
Teratoma	14	1	15
Seminoma	0	3	3
Nonseminoma	0	4	4
Total germ cell	14	8	22
Vascular tumors			
Hemangioma	3	0	3
Hemangiopericytoma	1	0	1
Total vascular	4	0	4
Miscellaneous			
Leiomyoma	6	0	6
Mesothelioma	1	3	4
Thyroid adenoma	4	0	4
Undifferentiated carcinoma	0	4	4
Germ cell tumor	0	1	1
Parathyroid adenoma	1	0	1
Fatty tissue	1	0	1
Sarcoma	0	2	2
Gastric duplication	1	0	1
Chemodectoma	1	1	2
Lymphangiosarcoma	0	1	1
Normal fatty tissue	1	0	1
Total miscellaneous	16	12	28
Grand total	146	84	230

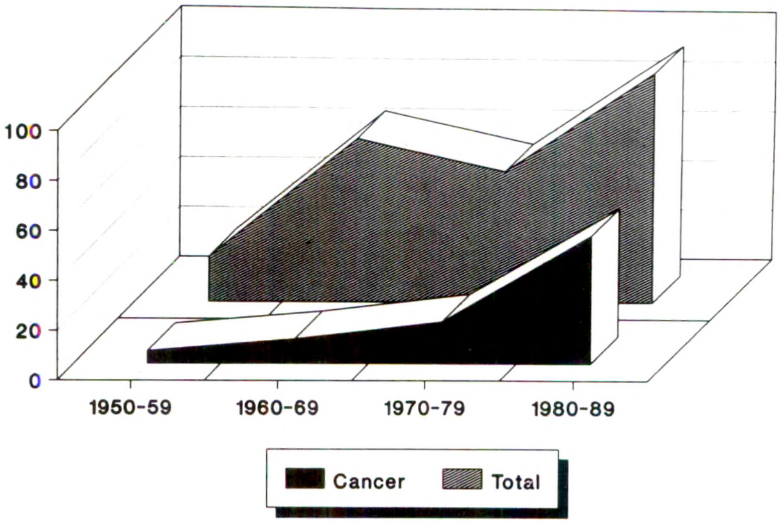


Fig 1. Primary mediastinal cysts and tumors operated on at Walter Reed Army Medical Center. The increasing number of patients with the lesions as well as the significant increase of malignant lesions is noted. One patient operated on in 1944 is included.

significant increase in the prevalence of malignancy in group 2 (69/146 versus 15/84; $p < 0.0001$). There was a significant increase in the number of lymphomas seen in group 2 (3/84 versus 33/146; $p < 0.001$) (Fig 2). There was no significant change in the number of neurogenic tumors seen, but a significant increase was noted in the number of malignant neurogenic tumors seen in group 2 (1/84 versus 10/146; $p < 0.01$). There were no significant changes in the number of benign or malignant thymic or germ cell tumors.

Anatomical Location

For the whole series, 131 (57%) of the patients had tumors in the anterior mediastinum, of which 66 were malignant and 65 were benign. Common tumors in the compartment included thymomas, lymphomas, and teratomas. There were 22 tumors in the middle mediastinum, 5 malignant tumors and 17 benign tumors. These consisted primarily of bronchogenic and pericardial cysts. The most common malignancy of the middle mediastinum was Hodgkin's lymphoma. In the posterior mediastinum, there were 77 tumors, 13 malignant tumors and 64 benign tumors. Common tumors included neurogenic tumors, enteric and bronchogenic cysts, and leiomyoma.

Comparing group 1 with group 2, there were no significant changes in the number of tumors in each compartment. However, there was a significant increase in malignant lesions in the anterior mediastinum (13/42 versus 53/89; $p < 0.005$) and posterior mediastinum (1/35 versus 12/42) ($p < 0.005$) in group 2.

Symptoms and Signs

The symptoms and signs in our series are shown in Table 2. There were 129 (56.1%) symptomatic patients in our series. Of the patients with malignant disease, 77.3% were symptomatic. Only 64 (43.9%) patients with benign disease were symptomatic. Common symptoms in patients with these tumors included chest pain or respiratory symptoms. Twenty-one patients had a constellation of symptoms including respiratory symptoms and chest pain. There were a total of 51 (22.2%) patients who had signs related to the tumor. In patients with malignant

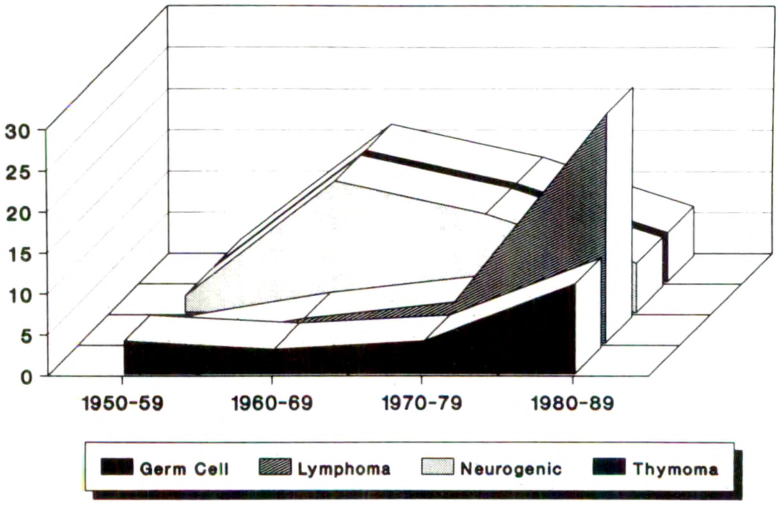


Fig 2. The incidence of solid primary mediastinal tumors with time is demonstrated. The significant increase in the incidence of lymphoma is noted. Lymphoma is the most common mediastinal mass seen at our institution this decade. One patient operated on in 1944 is included.

Table 2. Symptoms and Signs in Patients With Primary Mediastinal Cysts and Tumors

Symptom or Sign	Benign	Malignant	Total
Symptoms			
Asymptomatic	82	19	101
Respiratory symptoms[a]	23	17	40
Chest pain	23	20	43
Malaise	1	2	3
Dysphagia	4	0	4
SVCS	0	4	4
Combined[b]	6	15	21
Miscellaneous	7	7	14
Physical Examination			
Normal	122	57	179
Weight loss	3	3	6
Adenopathy	0	4	4
Respiratory signs[c]	4	2	6
SVCS signs	0	8	8
Neurofibromatosis	1	0	1
Neurological	5	2	7
Pericardial tamponade	0	1	1
Enlarged thyroid	2	0	2
Miscellaneous	9	7	16
Total	146	84	230

[a] Respiratory symptoms included shortness of breath, cough, and hemoptysis. [b] Combined symptoms included a constellation of symptoms, most commonly combined pain and respiratory symptoms. [c] Respiratory signs included rales, dullness to percussion, and wheezing.

SVCS = superior vena caval syndrome.

disease, 32.1% of the patients had signs related to the tumor. In patients with benign disease, 16.4% of the patients had such signs (p = not significant).

Most of the common signs and symptoms were evenly distributed between malignant or benign tumors. Signs and symptoms of superior vena caval syndrome were found in 12 patients, all with malignant disease. In comparing group 1 with group 2, there is a significant increase in the number of patients with symptoms (42/84 versus 87/146) in group 2 ($p < 0.05$). There was no significant change in the number of symptomatic patients with malignant disease.

Size

The size of the tumor was available in 148 patients. The mean size of the tumor for the series was 7.64 ± 3.9 cm (range, 1.5 to 20 cm). In group 1, the mean size was 7.52 ± 4.1 cm; in group 2, it was 7.7 ± 3.84 cm (p = not significant).

Diagnostic Studies

All patients in this series underwent chest radiography as an initial diagnostic investigation. Various other studies were obtained, most commonly, computed tomography. The effect of computed tomographic scanning can be seen in Figure 3. The introduction of computed tomography in 1979 clearly showed an increase in total studies obtained and a decrease in the relative number of studies done excluding computed tomography. There was a significant increase in the number of patients studied by means other than chest radiography (55/84 versus 35/146) in group 2 ($p < 0.0001$).

Predictors of Malignancy

Factors evaluated as predictors of malignancy included sex, age, date when first seen, compartment of the mediastinum, race, size, symptoms, signs, and laboratory data. Logistic regression analysis demonstrated a later operative date ($p < 0.001$), the presence of the tumor in the anterior mediastinum ($p < 0.001$), the presence of symptoms related to the tumor ($p < 0.01$), and the tumor size ($p < 0.001$) all to be associated with the presence of malignancy. Presence of physical signs related to the tumor, race, age, size, sex, and laboratory data were not predictive of malignancy.

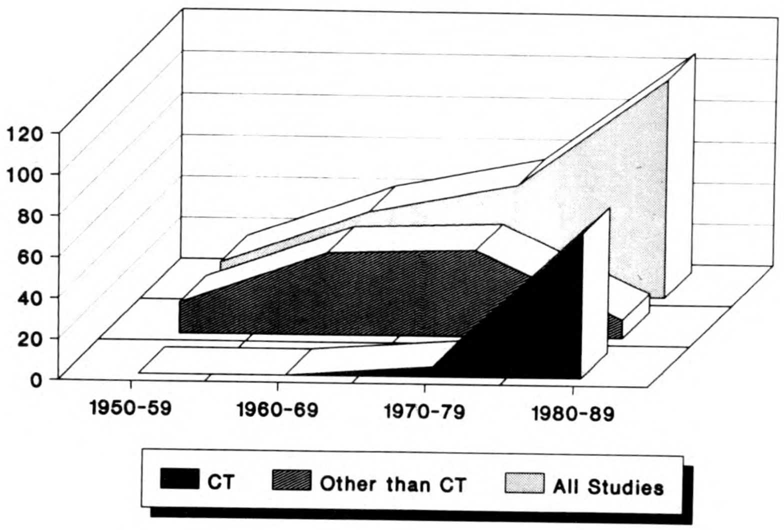


Fig 3. Diagnostic studies in addition to chest radiography used to evaluate patients with primary mediastinal cysts and tumors. One patient operated on in 1944 is included. (CT = computed tomography.)

Surgical Approach

The surgical approach to our patients included median sternotomy in 53 patients (23%), posterior lateral thoracostomy in 130 patients (56%), and anterior thoracotomy in 16 patients (7%). An anterior mediastinotomy or cervical mediastinal exploration was the only procedure used in 27 (11.7%) patients. Four patients had other procedures, which included cervical incisions (for a thymic cyst and a very superior neurilemoma) and a posterior midline approach for a giant cell tumor and neuroblastoma.

Comparing group 1 with group 2, there was a significant increase in the use of median sternotomy for anterior masses in group 2 (9/84 versus 44/146; $p < 0.005$) as well as a significant increase in the use of anterior mediastinotomy or cervical mediastinal exploration as the only procedure for anterior tumors in group 2 (1/84 versus 23/146; $p < 0.0001$).

Procedure

A total excision of the tumor was performed in 141 patients, of whom 125 had benign tumors and 16 had malignant tumors. A total resection including adjacent structures was performed in 16 patients, 6 with malignant and 10 with benign disease. Subtotal resection was performed in 24 patients, 18 with malignant and 6 with benign tumors. Forty-eight patients underwent biopsy only, of whom 44 had malignant and 4 had benign tumors.

All but 10 benign lesions were totally excised. These included biopsy in 4 patients. Three patients had benign-appearing thymic lesions. Pathology in these patients included thymic hyperplasia, ectopic normal thymus, and fatty tissue. The fourth patient had a huge nonresectable venous hemangioma [6]. Incomplete excision was performed in 6 patients: 4 with neurogenic tumors, 1 with a neuroenteric cyst, and 1 with a bronchogenic cyst.

For malignant lesions, the procedure and treatment varied according to the lesion. Twenty-nine patients with lymphoma underwent biopsy. Four patients with lymphoma underwent complete resection.

Morbidity and Mortality

There were six perioperative deaths in our group. Five patients had malignant disease and 1, who was moribund due to hypoxia secondary to airway compression when first seen, had a neuroenteric cyst. Of the 5 patients with malignant disease, 2 children died intraoperatively from inability to ventilate. Thus, three of the deaths occurred in desperately ill children in severe respiratory distress, taken to the operating room emergently. The 3 other patients survived the operating room but died of uncontrolled malignancy in the perioperative period. All deaths in the series occurred in group 2 ($p = 0.1462$). There were 10 major complications and 37 minor complications in the series. The morbidity in the series is listed in Table 3. There was not a significant decrease in morbidity from group 1 to group 2.

Table 3. Complications of Operation for Primary Mediastinal Cysts and Tumors

Complication	Group 1	Group 2	Total
Minor			
Pulmonary[a]	7	8	15
Urinary tract infection	1	1	1
Pericarditis	1	0	1
Horner's syndrome	3	0	3
Elevated diaphragm	4	5	9
Wound infection	3	1	4
Recurrent nerve paresis	1	0	1
Postoperative appendicitis	0	1	1
Keloid	1	0	1
Total minor complications	21	16	37
Major			
Paraplegia	0	1	1
Intraoperative hypotension	0	1	1
Chylothorax	0	1	1
Wound dehiscence	1	1	2
Myocardial infarction	1	0	1
Pulmonary embolus	1	1	2
Transfusion reaction	1	0	1
Sepsis	0	1	1
Total major complications	4	6	10

[a] Pulmonary complications included pneumothorax, pneumonia, and atelectasis requiring bronchoscopy.

Follow-up

Follow-up is available on 157 (68.2%) patients. Ninety-five patients had benign disease, and follow-up ranged from 2 months to 14 years. There was no recurrence, malignant degeneration, or growth of any tumor. One patient had chest pain from her median sternotomy that persisted over 2 years. Of neurological complications that occurred, five persisted on follow-up. These included a paralyzed vocal cord at 3 months, Horner's syndrome at 1 year (2 patients), an ulnar palsy at 7 years, and an elevated diaphragm at 2 years. Persistent gastritis requiring antacids developed in 1 patient after resection of a leiomyoma.

Follow-up is available in 62 patients with malignant disease and extended from 2 months to 22 years. Five patients died in the perioperative period. Seventeen died of their disease during follow-up. Cause of death included lymphoma, 5 patients; neuroblastoma, 3; sarcoma, 3; mesothelioma, 2; and chemodectoma, malignant teratoma, squamous cell carcinoma of the thymus, and seminoma, 1 each.

One patient with seminoma died 7 years postoperatively of a myocardial infarction. There was no evidence of recurrent disease on autopsy. Of the remaining 39 patients, 4 patients are alive with disease, including 3 patients with lymphoma and 1 with nonseminomatous germ cell tumor. Two patients, 1 with seminoma and 1 with lymphoma, are currently receiving chemotherapy and responding favorably. The remaining 33 patients are free of disease. Of this group, 1 patient had radiation pneumonitis and the remainder are symptom free. Life-table analysis demonstrated a 5-year survival of 45% for all patients with malignant disease.

Comment

Our series of 230 primary cysts and tumors of the mediastinum represents the third largest published report of such surgical series [1, 7]. The referral patterns to this hospital have been constant throughout this series. As a tertiary referral center for the military and its dependents, our service is exposed to a broad cross-section of the American population. These factors combined to make our population a good one in which to study the change of patients with these tumors over time.

The distribution of tumors in this series is similar to that of other large series. Although most series find neurogenic tumors to represent the largest group of mediastinal tumors [8–10], we and others find thymic tumors to be most common [1, 11]. Lymphoma represented 15.7%, which is consistent with other reported series [1, 8, 9, 11, 12].

There has been a large increase in the overall number of tumors seen during the last 20 years of our study. Further, there was a highly significant increase in the number of malignancies (see Fig 1). Analysis of these data shows this increase of malignant tumors to be due to the significant increase in patients with lymphoma (see Fig 2) and malignant neurogenic tumors. No increase in the number of malignant thymomas or germ cell tumors could be demonstrated. The relative increase of germ cell tumors and thymomas reported by Davis and associates [1] may represent the increased referral to Duke University of patients with myasthenia gravis and germ cell tumors as stated in their report.

56.1% of our population was symptomatic when first seen, consistent with other reports in the literature [10–14]. As in these other reports, respiratory symptoms and chest pain were the most common symptoms in our series. The increase of symptomatic patients seen at our service probably reflects an increase in the number of patients with malignant disease. A previous military series reported by Fontenelle and co-workers [12] with an unusually high incidence of asymptomatic patients has been explained in the literature by a patient population in military service where screening chest radiography is mandatory and repeated. Our data cannot support this finding. Among our 101 active-duty patients, 51 (50.4%) were symptomatic when first seen.

Physical signs related to mediastinal tumors have not been well defined in previous studies. In our series, a quarter of the patients had physical signs related to the tumor. As with symptoms, more patients with malignant disease have physical signs related to the tumor.

Diagnostic evaluation of mediastinal masses includes a posteroanterior and lateral chest roentgenogram. After this, a variety of invasive and noninvasive ancillary studies have been used to evaluate these masses. Computed tomography has changed the approach of this evaluation [1, 15]. In our study, the introduction of computed tomography is clearly noted by a reduced percentage of patients studied by means other than computed tomography.

Angiography has not been required at our institution to evaluate mediastinal tumors since 1983. However, the hope that computed tomographic scan would reduce ancillary studies in such patients has not materialized. Our study demonstrates a significant increase in the use of all ancillary studies from group 1 to group 2. Computed tomography has been the major contributor to this phenomenon (see Fig 3). Of particular note are 19 patients who had ancillary studies in addition to computed tomography and chest radiography. The ability of computed tomographic scan to influence the course of treatment in patients with these masses has been questioned [2].

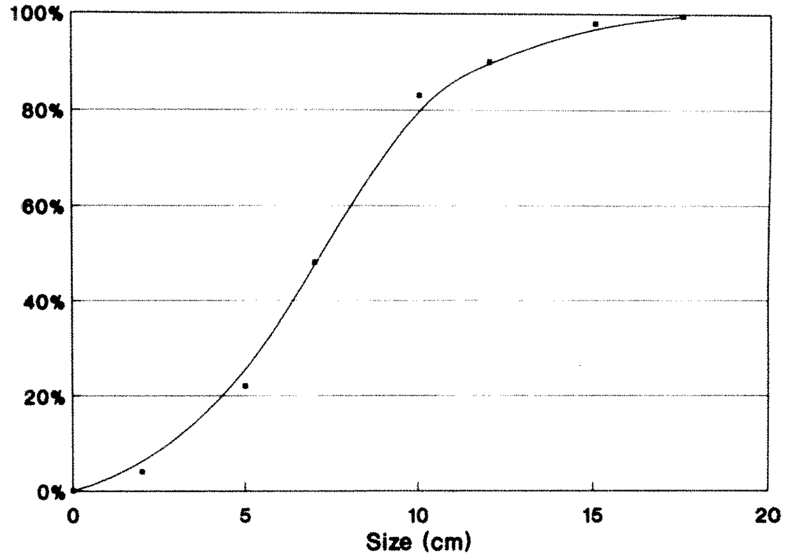
Logistic regression analysis to determine risk factors for malignancy in patients with mediastinal tumors appears to be valuable. Symptoms have been shown in multiple studies to be more common in patients with malignant disease [1, 3, 4, 6, 16, 17]. The anterior compartment as a risk factor for malignancy probably reflects the acute increase in the number of lymphomas seen in the last decade.

The increased risk of malignancy with increased size of the tumor has not been previously reported. The size of tumors has not changed significantly from group 1 to group 2, such that this factor is probably independent of time. Size was particularly predictive of malignancy in symptomatic patients with tumors in the anterior mediastinum (Fig 4).

The surgical approach to these tumors has changed significantly with time. The significant increase in median sternotomy for patients with anterior tumors probably reflects the increased comfort of thoracic surgeons with this incision and parallels its increased use for pulmonary operations [18, 19]. The use of cervical mediastinal exploration and anterior mediastinotomy as the only surgical procedure necessary for patients with anterior mediastinal tumors has greatly increased as well. Wychulis and associates [7], in 1971, decried "the use of mediastinoscopy and other indirect means of establishing a diagnosis because they are procedures without therapeutic merit." This is clearly no longer the situation. Increased numbers of lymphoma, effective nonsurgical therapy for lymphoma, and changes in the primary mode of therapy for germ cell tumors have all contributed to this change [20].

All the perioperative deaths in this series were in group 2. Death was related either to the inability to ventilate pediatric patients with large masses or progression of malignant disease despite appropriate treatment. The risk of respiratory compromise in pediatric patients with large mediastinal masses has been previously described [21].

The mobility of the military population makes follow-up particularly difficult. This is reflected by our ability to follow up only 68% of our patients. Despite this limited follow-up, two points are noteworthy. First, resection of benign lesions resulted in long-term relief of symptoms and no recurrence. Long-term morbidity in these patients was small, supporting surgical resection as the therapy of



Wilcoxon rank test (p<.001)

Fig 4. Logistic regression model demonstrating the predictive value of size in determining the malignancy of a lesion for symptomatic patients with anterior mediastinal masses.

choice for these lesions. Second, of patients with malignant disease, 33 of 62 are free of disease and 32 are symptom free at last follow-up.

With improved therapeutic regimens and better irradiation techniques, these results should only improve. These results strongly favor an aggressive therapeutic approach to primary mediastinal malignancies.

In conclusion, this series indicates that the spectrum of patients with mediastinal masses has changed in the last two decades. There appears to be an increase in malignant disease, an increase in tumors in the anterior compartment, and a particularly large increase in the number of mediastinal lymphomas. The fact that similar changes have been noted in other recent reports [1] suggests that these findings reflect true changes in the clinical spectrum of patients with mediastinal tumors.

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DISCUSSION

DR ROBERT M. SADE (Charleston, SC): In what way do you think you can account for the change in incidence of malignancy over time during your study?

DR EDWARDS: We believe there has been a real change in the spectrum of disease over the last two decades. As I pointed out in the presentation, there are some close similarities between our series and the Duke series, even though these two institutions have very different referral patterns. Both series confirmed a recent increase in malignant mediastinal disease, and both series found a relative increase in lymphomas over the last 20 years, which offers some fairly strong evidence that the nature of the disease has truly changed.

DR KAMAL A. MANSOUR (Atlanta, GA): I have difficulty understanding the high incidence of malignancy in neurogenic tumors after 1970. In our experience, and I am sure in the experience of others, the most common posterior mediastinal tumor is the benign neurilemoma. Do you have an explanation for the high incidence of malignancy in your series?

I have two comments. This series is noted by the absence of thyroid and parathyroid tumors, which may be seen primarily in the mediastinum. In the Emory experience with a series of 573 patients who were explored for primary hyperparathyroidism, parathyroid tissue was found in the mediastinum in 64 patients, and sternotomy was carried out in 21 patients. The second point I would like to address is we encountered 2 patients with malignant thymomas in the anterior mediastinum whose initial symptom was severe chest pain radiating to the left shoulder. Both of them were admitted to the coronary care unit, and the diagnosis was only made on computed tomographic scan. Would that referred pain, anginal pain, suggest malignancy? It was suggestive in our series.

DR EDWARDS: In answer to your last question, the presence of symptoms was indeed one of the significant risk factors in our multivariate analysis. We found a reasonably strong correlation between the presence of symptoms and the presence of malignant disease.

As far as the parathyroid tumors were concerned, we found what we found and there were just not very many in this series. In regard to your question about the incidence of neurogenic malignancies, I should point out that for the entire series, most of our neurogenic tumors were benign, which is in keeping with your experience. On the other hand, in the last 20 years just over one half of our neurogenic tumors have been malignant. The recent Duke series also found a relative increase in the number of malignant neurogenic tumors.

DR JOHN P. CLARKE (Virginia Beach, VA): Dr Edwards, I noted that 57%, I believe, of your tumors were thymomas. Do you feel the diagnosis of malignancy versus benign may be changing with differing perceptions of what is a malignant thymoma over a period as long as this series has existed? There was a recent article in *The Annals* trying to get at this matter and the fact that age, sex, and presence of myasthenia really did not correlate at all with malignancy and thymic tumors, but that histological type and clinical findings at operation were the factors of most significance. We have had the experience of marked variation in response to operation when we reviewed some of our own patients. One tumor removed in 1982 we sent to four outstanding solid-tumor pathologists and we got four different diagnoses on that patient. I would contend that if you have 57% thymomas in your series and the series goes over 20 years or so, there may be a real difference in what is malignant and benign over that period of time and even right now.

DR EDWARDS: Fifty-seven percent of our tumors were in the anterior mediastinal compartment, and 25% of our tumors were thymomas. About half of the thymomas were malignant. Our criteria for malignancy did not depend on histological grading of any kind. We relied entirely on the findings at the time of operation. If there was gross invasion of the tumor, then we considered it to be malignant.

DR F. HAMMOND COLE, JR (Memphis, TN): I enjoyed the paper very much, particularly the excellent illustrative material.

I wonder if you could help me with our dilemma. We do tend to find ourselves going more to what you refer to as the staging procedure, but how do you decide which patients should be approached by primary excisional biopsy through a sternotomy or thoracotomy versus going with a Chamberlain or Carlens sampling approach initially?

DR EDWARDS: This is one of the most challenging questions in the current management of mediastinal masses: when to perform only biopsy and when to perform a median sternotomy to resect the tumor. The question has become particularly important because of the increased incidence of lymphomas, which, of course, should ideally undergo biopsy and be referred for chemotherapy and radiation therapy.

Our decision to perform biopsy rather than resect through a median sternotomy is based on several criteria. First, the patient should have a tumor that can be reached by the standard mediastinoscopy or mediastinotomy procedures. Second, there should be no radiographic criteria that strongly suggest a nonlymphomatous tumor, ie, a cystic lesion or calcification consistent with a teratoma. Third, the patient should have a clinical presentation compatible with a lymphoma.

DR ALEX HALLER (Baltimore, MD): I noticed that the mortality was in those 3 children with anterior mediastinal masses who had anesthetic deaths. Four years ago, we reviewed our experience with anterior mediastinal masses in children with airway symptoms because we had anguishing experiences with them during anesthesia induction, particularly when the patient was paralyzed and there were changes in intrathoracic pressure dynamics.

On the basis of that experience, we recommended that such patients be treated with either irradiation or steroids or both without a histological diagnosis. Our oncologists were obviously upset and nervous about this approach, but when we showed them the morbidity and mortality associated with anesthesia and operation on that type of patient, they agreed to this new protocol. Over the last 4 years we have been using it. It has worked very well. We have not had any mortality; of course, that is just a short period of time, but during that time we have treated another 22 patients with symptoms of serious upper airway obstruction in whom we were worried about induction. In those patients, we have been able to make the diagnosis a few weeks to a month or so later after the tumor shrinks, as practically all the lymphomas will; many other tumors will also shrink with one or both of these modalities. Treatment has not changed the histology. My oncologists tell me it is more difficult to get their cell marker studies, but what good are cell markers if the patient is dead?

So, we are now using that approach, and I wonder if you have tried this or how you feel about that particular group of patients.

DR EDWARDS: In fact, that is exactly what we are doing these days. Two of the patients who died arrived at the hospital in some form of serious distress, and I think that if we were to see those patients today we would recommend radiation therapy rather than operation. The third patient was moderately symptomatic. We did preoperative flow loops and several other studies, all of which were normal. In retrospect, this patient probably died of tumor compression of the pulmonary artery rather than airway compromise.

Our present approach to the patient with a large symptomatic anterior mediastinal mass is to use radiation therapy as the initial mode of therapy.

Circulatory Support 1991

The Second International Conference on Circulatory Support Devices in End-Stage Heart Disease

San Francisco Marriott Hotel, San Francisco, California
November 15–17, 1991 (weekend meeting)

Circulatory Support 1991 will be a comprehensive multidisciplinary meeting focusing on the clinical applications of the entire spectrum of circulatory support devices. Surgeons, cardiologists, anesthesiologists, intensivists, perfusionists, engineers, and operating room and intensive care nurses are encouraged to attend as individuals or as a team.

The meeting is sponsored by The Society of Thoracic Surgeons under the direction of its Committee on Circulatory Assist Devices and Artificial Hearts. Committee members are: D. Glenn Pennington, MD, Chairman; Jack G. Copeland, MD; Charles Hahn, MD; J. Donald Hill, MD; George J. Magovern, MD; Peer M. Portner, PhD; and Glenn Rahmoeller.

For this weekend meeting, the Saturday morning segment entitled "Problem Cases" will include panel and audience discussions of four major subject areas: patient selection; anticoagulation management, bleeding, and thromboembolic risk; infections—prophylaxes and treatment; and management of secondary organ dysfunction. An outstanding international panel has been chosen to represent a broad spectrum of opinions for each subject.

Late Saturday morning and early afternoon, video sessions on the working details and proposed indications for support devices that are currently in use or development will be presented. A report of the current circulatory support device registry will be given. Breakout sessions of smaller groups will follow and focus on how to use external nonpulsatile circulatory support, external pulsatile circulatory support, and internal pulsatile circulatory support.

The Sunday sessions from 7:45 AM to 1:00 PM will be devoted to state-of-the-art presentations covering: emergency resuscitation techniques, heparinless bypass, the Hemopump experience, postoperative use of the Biopump, the VAD experience in Japan, optimizing hemodynamics and assessing myocardial recovery, right heart management during LVAD support, circulatory support in children, bridge to transplantation with the Thoratec VAD and with the Symbion TAH, chronic support with the TCI left ventricular assist system, the Novacor left ventricular assist system, and the Penn State TAH.

Poster presentations concerning a wide variety of subjects related to circulatory support as well as commercial exhibits demonstrating currently available devices will be available during breaks. Full CME credit will be provided for attendees.

The deadline for submission of poster abstracts is August 1, 1991. For further information and guidelines on poster abstract submission and other available meeting information, contact: The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; telephone: (312) 644-6610.

Site of Action of Continuous Extrapleural Intercostal Nerve Block

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Continuous extrapleural intercostal nerve block has been shown in a randomized, controlled study to be effective in reducing postoperative pain after thoracotomy and in restoring pulmonary mechanics. To assess the extent of spread of bupivacaine infused through an extrapleurally placed cannula inserted at thoracotomy, iohexol (Omnipaque) was infused at 5 days postoperatively in 5 patients and computed tomography performed. The contrast medium was confined to the paravertebral space covering on average six intercostal spaces. This study demonstrated that anatomically, the site of action of the bupivacaine infused through an extrapleural cannula was primarily in the paravertebral space.

(Ann Thorac Surg 1991;51:387–9)

We have previously demonstrated the effectiveness of continuous intercostal nerve block for postthoracotomy analgesia [1]. A prospective, randomized, double-blind, placebo-controlled trial confirmed the efficacy of this method not only in relieving postoperative pain after thoracotomy but also in reducing the early loss of postoperative pulmonary functions and restoring pulmonary mechanics [2]. The spread of the bupivacaine was demonstrated intraoperatively by the use of methylene blue [1, 2]. We now report our study on the postoperative anatomical distribution of contrast medium infused through an extrapleural cannula.

Patients and Methods

Five patients undergoing thoracotomy for esophageal resection (n = 2), lobectomy (n = 2), and antireflux procedure (n = 1) were studied. The technique of insertion of the extrapleural cannula has been previously described [1, 2]. The essential steps are as follows. At the end of the operation before the chest is closed, the parietal pleura is raised medially as far as the vertebral bodies. A percutaneous epidural cannula is inserted through a 16-gauge disposable Tuohy (Portex Ltd, Hythe, UK) needle. A small defect is made in the extrapleural fascia using Lahey's forceps and the tip of the cannula is passed directly into the paravertebral space. A bolus injection of 20 mL of 0.5% bupivacaine is first given. This is followed by a continuous infusion of the same solution at a rate of 0.1 mL/kg body weight per hour.

The efficacy of this technique was confirmed in a randomized, controlled study in 80 patients, including 56 patients previously reported [2].

On the fifth postoperative day, when patients had become more mobile, a dose of Omnipaque 300 (iohexol; Winthrop Pharmaceuticals, NY) equivalent to the hourly rate of the bupivacaine was infused through the cannula with the patients sitting upright. At the end of this hour, computed tomographic scanning in two axes was performed to demonstrate the spread of contrast medium.

Results

There were no complications related to either the insertion of the cannula, infusion of bupivacaine, or infusion of radiopaque contrast medium in these patients. The efficacy of the method in postthoracotomy analgesia and the favorable effects on pulmonary mechanics were equivalent to those previously reported [2]. The pain scores were lower on each postoperative day in patients receiving bupivacaine infusion compared with those receiving saline solution ($p < 0.001$) (Fig 1). The forced expiratory volumes in 1 second were significantly greater in patients receiving bupivacaine ($p < 0.001$) (Fig 2). Similar trends were seen in the forced vital capacity and peak expiratory flow rate. The incidence of postoperative pulmonary complications was lower in the bupivacaine group even in those patients with chronic obstructive airway disease.

Figures 3 and 4 show the transverse and coronal planes on computed tomographic scanning, confirming the unilateral paravertebral spread of contrast medium. This spread covered an average of six intercostal spaces (range, five to seven) without overspill into the pleural cavity or medial spread into the epidural spaces.

Comment

Patients undergoing thoracotomy experience severe postoperative pain and marked respiratory impairment [3, 4]. Pain is the most important factor responsible for the decrease in respiratory reserve occurring after operation [5]. The use of narcotic drugs either by the intramuscular or intravenous routes may be effective in achieving pain relief. However, respiratory depression may be exacerbated [6]. Even with narcotic doses that do not depress ventilation the natural sigh mechanism is obtunded, thereby contributing to atelectasis [7]. Epidural analgesia

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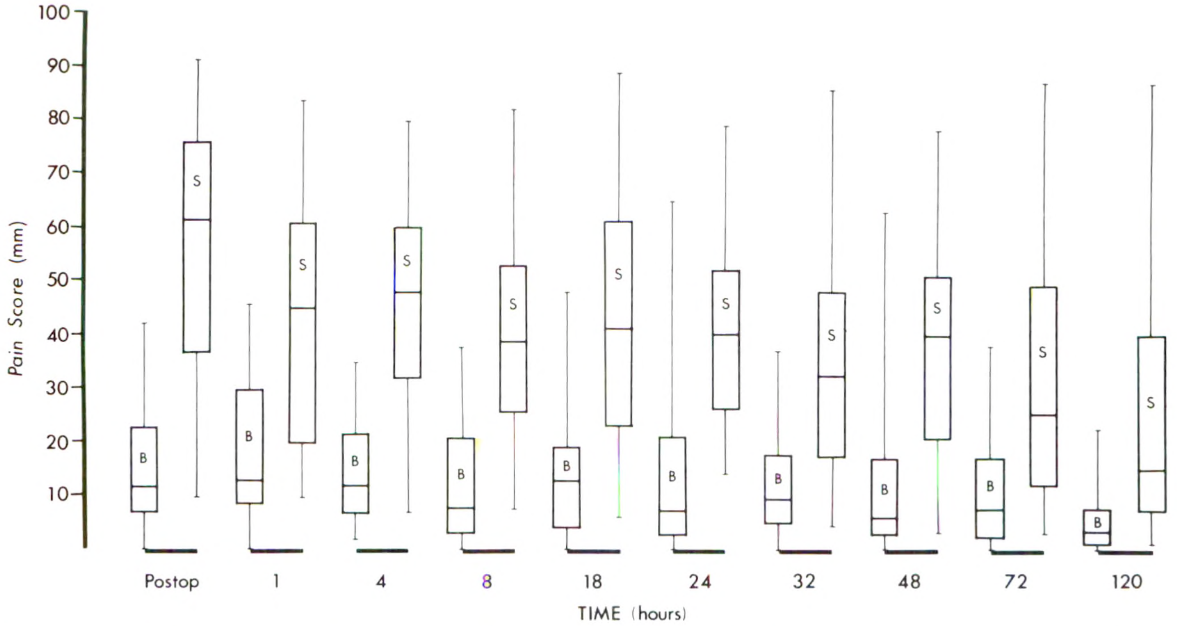

Fig 1. Box and whisker plot of pain scores (median, interquartile range, and range) on each postoperative day. For each day scores in the bupivacaine group (B) *were lower than those in the saline solution group* (S) *(p < 0.001).*

[3] and intercostal nerve blocks [4, 8] have been consistently shown to provide satisfactory pain relief and to aid recovery of pulmonary functions. Epidural blocks, however, still carry serious complications including that associated with bilateral sympathetic blockade in the upper thoracic region with resulting hypotension [9]. We have not encountered such complications in our experience with continuous extrapleural intercostal nerve block in more than 300 patients. We have demonstrated in this study the unilateral nature of the paravertebral block achieved with the extrapleurally placed cannula. With refinement of the technique of insertion [10], precise spread of the bupivacaine is ensured.

The segmentation of the intercostal nerves in small bundles lying freely in the paravertebral space without any enclosing fascial sheath exposes the nerves favorably for blockade [11]. Furthermore, much of the pain after thoracotomy is due to straining from rib retraction of the ligaments of the costavertebral and costotransverse joints and the posterior spinal muscles, which are supplied by posterior primary rami [12]. Paravertebral block effectively

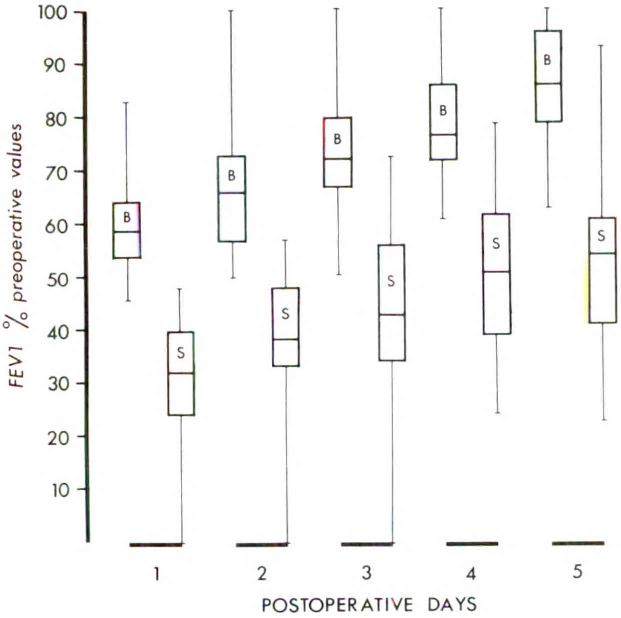

Fig 2. Box and whisker plot of forced expiratory volume in 1 second (FEV1) *expressed as a percentage of preoperative value. Values in the bupivacaine group* (B) *were higher than those in the saline solution group* (S) *on each day (p < 0.001).*

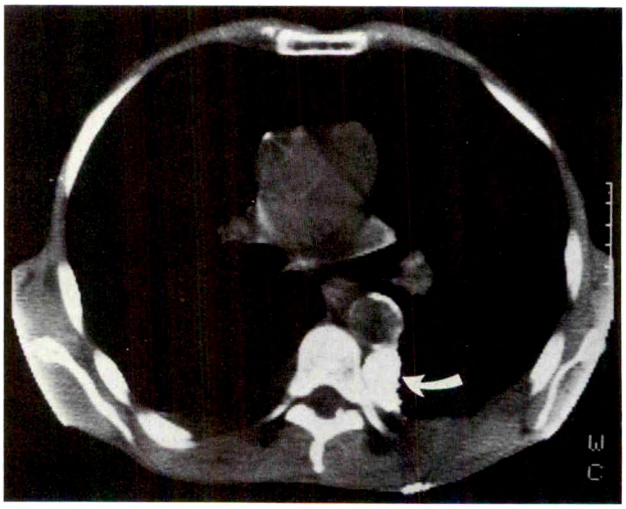

Fig 3. Computed tomographic scan (transverse plane) showing contrast medium in paravertebral space (arrow).

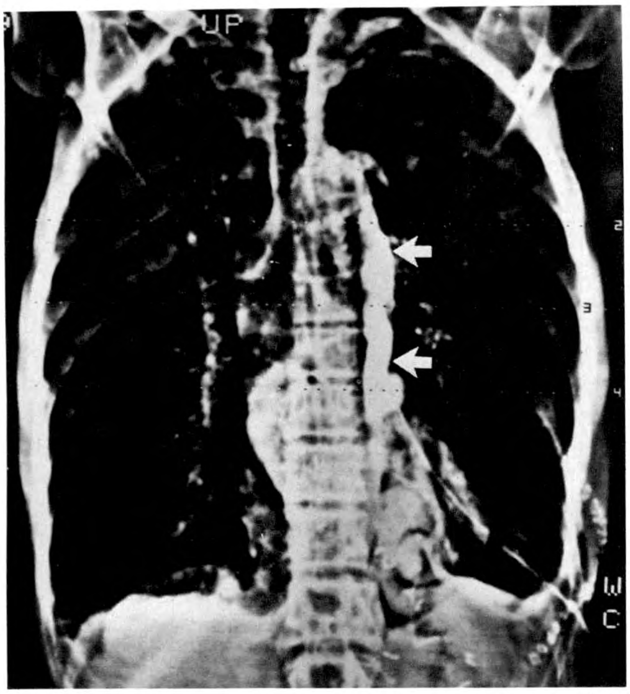

Fig 4. Computed tomographic scan (coronal plane) showing spread of contrast medium over six spaces (arrows) *after left thoracotomy for esophagectomy.*

interrupts such pathways and would be more effective compared with more distal blocks with local anesthetic agents or cryoprobe neurolysis [13, 14].

The unilateral sympathetic block that accompanies intercostal nerve block reduces the hormonal and neural metabolic responses to operation [15]. Horner's syndrome may result as a consequence [16]. Of 300 patients to date we have encountered 4 in whom transient Horner's syndrome developed.

Although a percutaneous approach for the placement of a cannula within the paravertebral space has been described, a failure rate of 20% has been reported [17]. By placing accurately the cannula at thoracotomy, we have not encountered any difficulty either at insertion or during postoperative continuous infusion. Our study confirms the anatomical distribution of paravertebral block for effective postthoracotomy analgesia and beneficial effects on postthoracotomy pulmonary functions.

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Role of Percutaneous Fine-Needle Aspiration Biopsy in Suspected Intrathoracic Malignancy

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Percutaneous fine-needle aspiration (PFNA) biopsy is an accepted technique for the diagnosis of suspected intrathoracic malignancy, but the appropriate indications for its use have not been clearly defined. To help establish guidelines, we performed a retrospective analysis of 188 patients who underwent PFNA biopsy for suspected intrathoracic malignancy. Biopsy led to a diagnosis in 72% (135/188) of the patients, but in 27% (50/188) samples were inadequate for cytological diagnosis, and in 2% (3/188) samples were adequate but failed to yield a diagnosis. Fifty-three patients underwent surgical intervention, thus allowing histological confirmation of the cytological diagnosis. In patients with a diagnosis from PFNA biopsy, operation confirmed malignancy in 97% (37/38) and a specific cell type in 79% (30/38). In patients without a diagnosis after biopsy, a malignancy was found in 73% (11/15) at the time of operation. This suggests a high rate of accuracy when PFNA biopsy provides a diagnosis. However, it also illustrates that a substantial percentage of PFNA biopsy attempts fail to yield a diagnosis in patients ultimately found to have malignancies. This implies that PFNA biopsy might best be reserved for patients who are not surgical candidates.

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Percutaneous fine-needle aspiration (PFNA) biopsy unquestionably has an important role in the diagnosis of pulmonary malignancies, primarily the more peripheral lesions, which are generally not accessible with bronchoscopy [1, 2]. The exact indications for the use of PFNA biopsy, however, remain a topic of discussion [3]. We retrospectively analyzed the results of 188 PFNA biopsies for suspected intrathoracic malignancy to determine the accuracy of this technique at its current level of use and to recommend appropriate guidelines for future use.

Material and Methods

The records of all patients who had undergone PFNA biopsy of intrathoracic lesions within a period of 5 years were reviewed. Twenty-one patients were excluded from the study because of clinical suspicions of an infectious etiology of the lesion. The remaining 188 patients constitute the study group. There were 81 female (43%) and 107 male patients (57%) ranging from 4 to 87 years old (median age, 62 years). Seventy-six patients (40%) had a history of malignancy.

All biopsies had been performed under the supervision of one of two experienced senior faculty radiologists. In general, 22-gauge free needles had been used, guided by either fluoroscopy or computed tomography. The reviewing cytologist had been present at the time of biopsy to ensure that a satisfactory sample had been obtained, and an experienced pathologist had judged the adequacy of the sample. A sample was judged adequate if it contained sufficient material to identify the presence or absence of malignancy as well as the cell type. The indications for percutaneous biopsy varied considerably, but the procedure was most often employed after sputum cytology and bronchoscopy failed to provide a diagnosis.

Results

Complications

Few complications were encountered. Pneumothorax occurred in 10 patients (5.3%), only 2 of whom required a chest tube. There were no major episodes of hemorrhage, and no deaths were attributable to the procedure. There were no other notable complications.

Biopsy Results

Overall, PFNA biopsy led to a diagnosis in 135 (72%) of the 188 patients. Among the 53 patients for whom biopsy did not lead to a diagnosis, 50 had inadequate samples for cytological interpretation, and 3 had adequate samples that failed to yield a diagnosis.

Fifty-three patients ultimately underwent operation, and this allowed correlation of histological and cytological specimens. For 38 (72%) of these 53 patients, PFNA biopsy had provided an overall diagnosis. Surgical intervention confirmed malignancy in 37 (97%) of these 38 patients and provided a specific cell type in 30 of the 38 (79% true-positive rate). In 2 of 3 patients, PFNA biopsy led to the accurate diagnosis of a benign process as benign. In the 1 remaining patient, PFNA biopsy resulted in an incorrect diagnosis of malignancy for a lesion that was found to be benign at operation. In the group having operation, there were no instances in which PFNA biopsy led to a misdiagnosis of a malignant process as benign.

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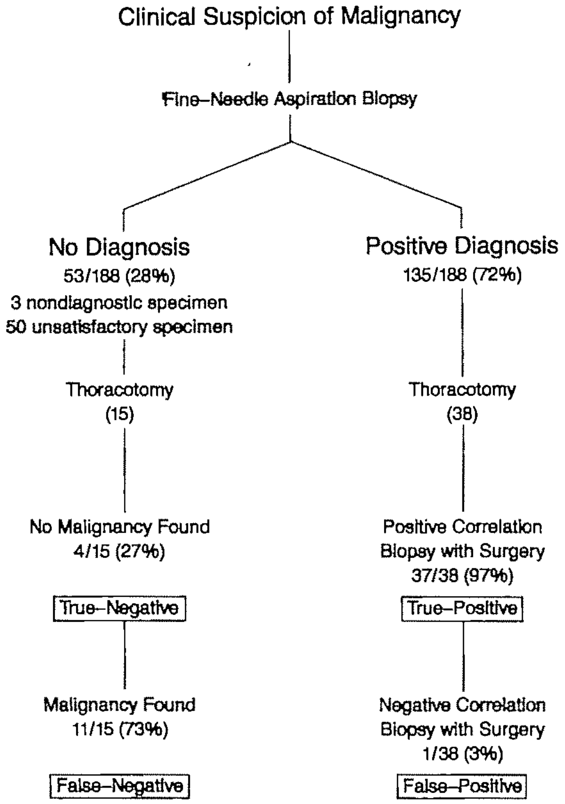

Fig 1. Summary of results.

Eleven (73%) of the 15 patients for whom PFNA biopsy did *not* result in a diagnosis were found to have a malignancy at the time of operation. No malignancy was found in the other 4 (27%). All 15 had nondiagnostic PFNA biopsy results because of inadequate specimens. Figure 1 summarizes these results.

Cell Types

Table 1 lists specific cell types encountered in the surgical group. An unusually high percentage of primary cancers were adenocarcinomas rather than the more common squamous cell carcinomas. Granulomas were found in the surgical specimens of 3 patients, and no disease was found in the specimens of 3 others. Table 2 compares the diagnoses resulting from surgical intervention and PFNA biopsy. The histologies of the patients who underwent operation after PFNA biopsy failed to lead to a diagnosis were as follows: squamous cell carcinoma, 3 patients; adenocarcinoma, 3; melanoma, 2; granuloma, 2; and small cell carcinoma, carcinoid, basal cell carcinoma, sclerosing mediastinitis, and no disease, 1 patient each.

Comment

The technique of percutaneous needle biopsy of intrathoracic lesions was developed in the 19th century. The original large-bore needles had a relatively high rate of morbidity and have now been replaced by safer fine-needle techniques. Advances in radiographic imaging technology and especially the development of cytopathology for the diagnosis of malignancy have also contributed substantially to the acceptance of percutaneous needle biopsy [1, 2].

Surgeons generally agree that the decision to use PFNA biopsy should be based on clear indications, especially the likelihood that the procedure will directly influence the management of the patient's disease [4, 5]. Most frequently, PFNA biopsy is reserved for patients for whom sputum cytology and bronchoscopy have failed to provide a diagnosis [6–9]. Controversy persists, however, as to the exact indications for the use of this procedure [3]. Percutaneous fine-needle aspiration biopsy has been advocated for the following groups of patients: patients with an intrathoracic lesion that can be imaged [10]; only patients who have operable disease [11, 12]; only patients who have inoperable disease [6, 13]; and only patients who are likely to have metastatic disease [7, 14]. Some authors [8, 15] have simply noted those conditions that would contraindicate the procedure.

We have sought to establish clear guidelines for the use of PFNA biopsy by documenting the accuracy of this technique. We also compared the experience of the University of California, Los Angeles, with PFNA biopsy of suspected intrathoracic malignancy with that found in the literature.

Safety

Percutaneous fine-needle aspiration biopsy results in few complications. Pneumothorax is the most prevalent, with an average reported incidence of approximately 25% (range, 12% to 35%) [4, 6, 7, 11, 12, 15–17]. Typically, half of those patients require chest tubes for resolution. Although there remains a theoretical risk that malignant disease might be spread by the needle traversing both

Table 1. Cell Types in the Surgical Group

Cell Type	No. of Specimens
Primary	
Adenocarcinoma	19
Squamous cell carcinoma	8
Small cell carcinoma	1
Large cell carcinoma	1
Mesothelioma	1
Poorly differentiated carcinoma	1
Carcinoid	1
Metastatic	
Adenocarcinoma	4
Melanoma	3
Sarcoma	2
Basal cell carcinoma	1
Wilms' tumor	1
Transitional cell carcinoma	1
Thymoma	1
Seminoma	1

Table 2. Comparison of Results of Percutaneous Fine-Needle Aspiration Cytology and Surgical Histology

	Cytology							
Histology	Adenocarcinoma	Squamous Cell Carcinoma	Large Cell Carcinoma	Melanoma	Mesothelioma	Sarcoma	No Malignancy	Other Malignancy
Adenocarcinoma (20)	17	0	0	0	0	0	0	3
Squamous cell carcinoma (5)	0	4	0	0	0	0	0	1
Large cell carcinoma (1)	0	0	1	0	0	0	0	0
Melanoma (1)	0	0	0	1	0	0	0	0
Mesothelioma (1)	0	0	0	0	1	0	0	0
Sarcoma (2)	0	0	0	0	0	2	0	0
No malignancy (3)	0	0	0	0	0	0	2	1
Other malignancy (5)	0	0	0	0	0	0	0	5

tumor and normal tissue [2, 18], very few cases have actually been documented, and virtually none have been reported since the introduction of smaller-caliber needles [6, 7, 15, 18–23]. Hemorrhage is an exceptionally rare complication, and it did not occur in our series.

Accuracy

In this study, PFNA biopsy led to a diagnosis in 72% of patients; in the remaining 28%, the biopsy specimens were unsatisfactory. Histological confirmation of disease was obtained in those patients who subsequently underwent thoracotomy. Admittedly, patients who later undergo operation are not necessarily a representative group. Nevertheless, the correlation for malignancy in those who had a PFNA biopsy diagnosis was 97%, and the correlation for a specific cell type was 79%. This high level of accuracy for PFNA biopsy is similar to that found by others. In a study of 181 patients, Winning and co-workers [13] reported an 86% accuracy for primary lesions, and Sagel and associates [6], in a review of 1,211 patients, had an accuracy rate of 87% after one PFNA biopsy attempt and 96% after two attempts. Many large reviews report similar results, with accuracy for diagnosing primary tumors ranging from 64% [8] to 97% [1, 5, 7, 8, 11, 12, 17, 20]. Accuracy appears to improve little after more than two biopsy attempts.

In the present study, 11 (73%) of the 15 patients for whom PFNA biopsy did *not* provide a diagnosis were ultimately found to have a malignancy at operation (See Fig 1). It therefore appears that a substantial number of PFNA biopsy attempts fail to yield a diagnosis. In the past, many studies excluded failed attempts [4, 5, 17], thereby falsely elevating the apparent accuracy of the procedure. The failure rate of PFNA biopsy diagnosis, however, is central for determining its contribution. We had a failure rate of 28%, and others [8, 11, 13, 17, 20] have noted a nondiagnostic PFNA biopsy rate ranging from 6.5% to 45% for suspected intrathoracic malignancy. Steenskov and colleagues [4] directly addressed the issue of negative PFNA biopsy results and found that although accuracy of positive PFNA cytology was 97.1%, "conclusive" data were provided by only 53.6% of specimens. Of those found to be conclusive, 27.4% were "decisive," ie, the results changed the management of a patient, whereas 26.2% were simply supportive of existing clinical suspicions. In that study, 44.8% of PFNA biopsy results were "inconclusive" and did not contribute to management. For the present study, Figure 1 indicates the true-positive, true-negative, false-positive, and false-negative rates for PFNA biopsy, not for the cytology itself, but rather to provide information *useful* in patient management.

Cell Types

Specific cell types are another important consideration when assessing the effectiveness and impact of PFNA biopsy. Many studies have reported the ability of this technique to provide a diagnosis that is "positive" or "negative" for malignancy. However, when considering the influence of PFNA biopsy on the management of a patient, information regarding cell type may often be of importance. In the present study, such information was available in the majority of patients (79%).

The diagnostic accuracy of PFNA biopsy appears to be excellent for small cell carcinoma [17, 24], but usually this can be clinically distinguished from other forms of primary lung cancer [25]. Because operation is not generally considered in the initial therapy for this disease, PFNA biopsy is an appropriate method for confirming this clinical suspicion.

Metastatic Lesions

Information regarding metastatic lesions may also be important in patient management, although information obtained by PFNA biopsy is often less accurate than that for primary tumors [5, 7, 11, 13]. Winning and associates [13] reported only 42% accuracy in the diagnosis of metastatic lesions and Sinner [12], 46.4% accuracy.

Benign Disease

The accuracy of PFNA biopsy in diagnosing benign disease is much less than that in diagnosing malignancy, and PFNA biopsy often fails to lead to a diagnosis [10]. A variety of factors can cause difficulty in interpreting PFNA samples, including granulomas, infarcts, inhaled or aspirated substances, some fungal infections, and changes owing to irradiation or various drugs [24–27].

Recommended Guidelines for Use of PFNA Biopsy

Because PFNA biopsy is an invasive procedure, it should be used in those situations where less invasive methods (ie, sputum cytology and bronchoscopy) have failed to provide a diagnosis. In general, PFNA biopsy should be reserved for patients who are not good surgical candidates. Such patients include those with extensive and clearly unresectable disease, clinically evident small cell carcinoma, poor general health precluding the risks of a major operation, and metastatic disease not amenable to resection. Under these circumstances, a diagnosis is sought to direct alternative therapy, ie, chemotherapy or radiation therapy.

Conversely, the results of PFNA biopsy are unlikely to alter the management of a patient who *is* a candidate for operation. In this circumstance, if PFNA biopsy leads to a diagnosis of malignancy, the patient will undergo thoracotomy. On the other hand, if biopsy does not provide a diagnosis, the patient will still require a thoracotomy, for both diagnosis and possible therapy.

In this study, we considered the overall success of the PFNA technique in altering patient management. The results, which correlate well with those reported in the literature, indicate that PFNA biopsy is very accurate when it provides a diagnosis—not only in determining the presence of a malignancy, but also in determining its cell type. However, we found that a considerable number of PFNA biopsy attempts fail to yield a diagnosis. Thus, although accuracy can be quite high, the actual influence on patient management may be much less. This is influenced greatly by patient selection, and therefore we advocate clear criteria, as outlined.

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Fibrous Skeleton and Ventricular Outflow Tracts in Double-Outlet Right Ventricle

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Twenty-four hearts in which both great arteries arose from the right ventricle were studied to establish variations present within the fibrous skeleton and infundibular morphologies. Variations were also noted in the location of the ventricular septal defect and measurements were obtained of the outlet septum and the circumferences of the arterial valves. Completely muscular subarterial infundibulums were present in only 9 (37.5%) of the hearts, with varying degrees of fibrous continuity between the leaflets of the arterial and atrioventricular valves in the remainder. The aorta was rightward and posterior in 12 (50%) of the hearts, and subaortic and subpulmonary ventricular septal defects were present in equal numbers in this group. No subaortic defects were present when the aorta was side-by-side and right-sided. No subpulmonary defects were present in hearts with a posterior aorta. The mean ratio of 0.91 ± 0.36 for the subpulmonary to subaortic length of the outlet septum was significantly less than the value of 1.54 ± 0.41 noted previously in hearts with tetralogy of Fallot ($p < 0.001$).

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In 1972, Lev and associates [1] propounded, on the basis of logical pathological and surgical considerations, a concept of defining the heart with double-outlet right ventricle in terms of the type and location of the ventricular septal defect. This concept excluded from consideration neither those hearts with incomplete origin of both arterial trunks from the right ventricle (provided the majority of both arterial circumferences arose from the right ventricle) nor those hearts with fibrous continuity between the leaflets of the arterial and atrioventricular valves. This was in contrast to the "prevalent concept at the present time" [1], namely that double outlet from the right ventricle should only be diagnosed when both arteries arose exclusively from the right ventricle, with the leaflets of each arterial valve supported exclusively by completely muscular infundibular structures.

Since then, subsequent morphological and surgical studies [2–5] have argued in favor of using the "50% rule" to define hearts having a double-outlet right ventricle ventriculoarterial connection. Controversy persists, nonetheless, with other authors [6, 7] still strongly supporting the restrictive definition of double-outlet right ventricle for cases with exclusively right ventricular origin of both great arteries in the presence of discontinuity bilaterally between leaflets of the arterial and atrioventricular valves.

In the light of this continuing debate, particularly because the concept of a bilateral infundibulum is held to represent prevailing opinion [6], we have studied the morphology of the ventricular outflow tracts in those hearts within our collection having exclusively right ventricular origin of both arterial trunks, comparing our findings in this respect with those of a similar study performed on hearts with tetralogy of Fallot [8]. This latter point is of major importance, because much of the debate concerning the role of infundibular morphology in categorization of double-outlet right ventricle centers upon the similarities and differences between such hearts and those with tetralogy of Fallot [6].

Material and Methods

Hearts were selected from the cardiopathological collection of the National Heart and Lung Institute, Brompton Hospital, London, choosing the 24 specimens with usual atrial arrangement, concordant atrioventricular connections, and, as judged by us, exclusive origin of both arterial trunks from the morphologically right ventricle. The study was limited, therefore, to those hearts in which there was no extension of an arterial trunk into the cavity of the left ventricle. In addition, hearts with the overall morphology of tetralogy of Fallot (subaortic ventricular septal defect and anterior deviation of the outlet septum with infundibular pulmonary stenosis) were excluded even if the aorta also arose exclusively from the right ventricle.

The 24 selected hearts were then studied with particular attention directed toward the morphology of the areas of fibrous continuity between the leaflets of the arterial and atrioventricular valves, the orientation and position of the great arteries, the type of ventricular septal defect, the dimensions of the outlet septum, and the circumferences of the great arteries, noting in this respect the presence of any subarterial infundibular stenosis. Integrity of the

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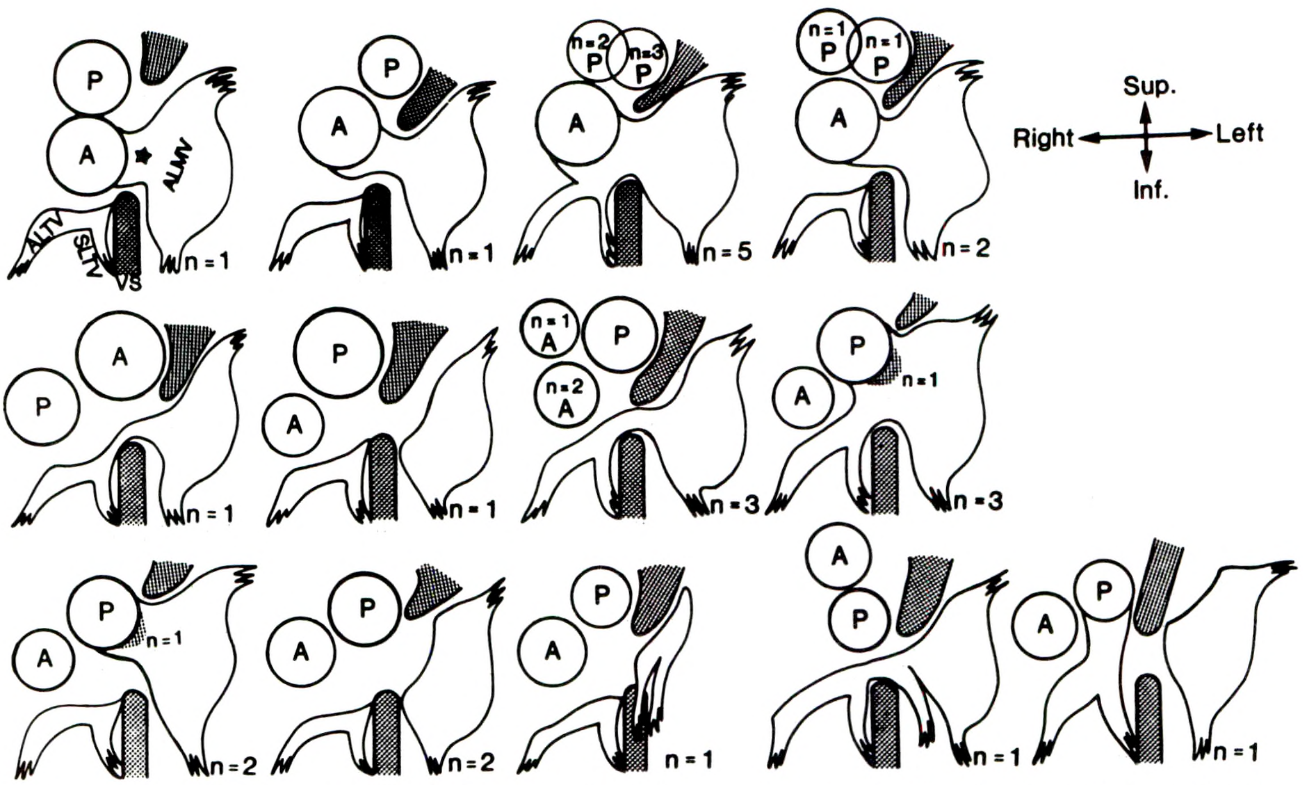

Fig 1. Schematic representation of patterns of morphology recognized in the hearts within this study, viewed from the ventricular aspect in the short axis. (A = aortic valve; ALMV = aortic leaflet of mitral valve; ALTV = anterosuperior leaflet of tricuspid valve; P = pulmonary valve; SLTV = septal leaflet of tricuspid valve; VS = ventricular septum; ★ = region of valvar fibrous continuity.)

specimen was another important factor in selection, and we excluded some that would otherwise have qualified but were excessively distorted by surgical or postmortem alteration. Measurements of the subaortic and subpulmonary infundibular lengths were taken from the crest of the outlet septum to the closest point of attachment of the leaflets of the arterial valves. Aortic and pulmonary internal circumferences were measured at the superior level of the attachment of the valvar leaflets. Ratios were derived for infundibular lengths and truncal circumferences by using the values for the aorta as the denominator.

Results

The basic patterns of morphology observed in the hearts are shown schematically in Figure 1. Of the 24 hearts examined, 15 (62.5%) exhibited some degree of continuity between the leaflets of the arterial and atrioventricular valves. Six (40%) of the 15 showed continuity between the pulmonary and atrioventricular valvar leaflets. One of these hearts displayed continuity only between the pulmonary and tricuspid valve, with a muscular ventricular septal defect being present in a noncommitted location (Fig 2). A further 9 hearts (60%) demonstrated continuity between the leaflets of the aortic and atrioventricular valves. In 1 heart with pulmonary–mitral valvar continuity, and in 1 with aortic–mitral continuity, the fibrous band between the leaflets was incomplete, a muscle bar of 3 to 4 mm being interposed between the attachments (Fig 3). Five of the remaining 9 hearts that did not have any fibrous continuity between the leaflets of the arterial and atrioventricular valves did, however, display continuity between the leaflets of the mitral and tricuspid valves (Fig 4). This is the criterion we use to designate a ventricular septal defect as being perimembranous in the setting of double-outlet right ventricle. The other 4 specimens exhibited discontinuity between all valvar structures. Taken together, only just over one-third of this selection of hearts satisfy the supposed "prevalent" [6] definition for the heart with double-outlet right ventricle, as exemplified by the specimen shown in Figure 4.

Within the overall series, the ventricular septal defect was subaortic in 9 hearts, subpulmonary in 7, and noncommitted in 7; the remaining ventricular septal defect was doubly committed in the presence of fibrous continuity between the leaflets of the aortic and pulmonary valves (Fig 5). The ventricular septal defects were perimembranous in 14 hearts, in that there was continuity between the leaflets of the mitral and tricuspid valves in the posteroinferior rim of the defect as described in the preceding paragraph (see Fig 4). The posteroinferior rim was muscular in the remaining 10 hearts, the ventriculo-infundibular fold fusing with the posterior limb of the septomarginal trabeculation to create discontinuity between the leaflets of the mitral and tricuspid valves. All hearts with aortic–mitral valvar continuity had subaortic or doubly committed ventricular septal defects, and all

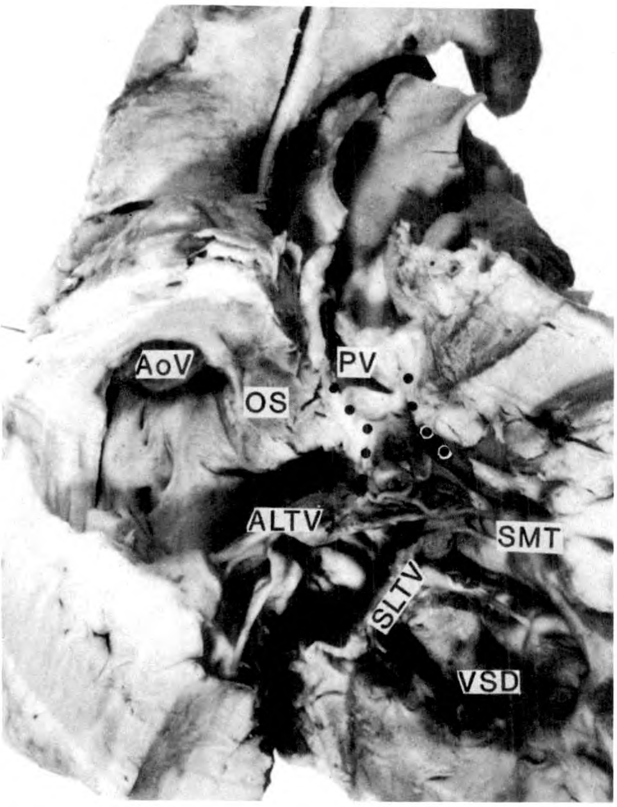

Fig 2. Specimen demonstrating fibrous continuity only between the leaflets of the pulmonary and tricuspid valves (stippled margin)*. A noncommitted defect is present within the trabecular septum.* (ALTV = *anterosuperior leaflet of tricuspid valve;* AoV = *aortic valve;* OS = *outlet septum;* PV = *pulmonary valve;* SLTV = *septal leaflet of tricuspid valve;* SMT = *septomarginal trabeculation;* VSD = *ventricular septal defect.)*

hearts with pulmonary–mitral valvar continuity had subpulmonary ventricular septal defects.

The position of the aorta relative to the pulmonary trunk is shown in Figure 6, with subdivision of the type of septal defects related to each aortic location. An aorta located rightward and posterior in relation to the pulmonary trunk was most common, being seen in 12 hearts (50%), followed by right (in side-by-side orientation) and posterior locations, with 5 hearts in each category. One heart had the aorta in a left-sided and anterior position, whereas 1 had a directly anterior aorta. Of the 5 hearts with a posterior aorta, all had aortic–mitral valvar continuity with subaortic ventricular septal defects (1 was doubly committed). The 2 hearts with anterior and left-anterior positioning of the aorta had noncommitted perimembranous ventricular septal defects and arterial–atrioventricular valvar discontinuity. No subaortic ventricular septal defects were found with rightward positioning of the aorta, and no subpulmonary defects were noted with posterior aortic location. None of the hearts had serious subpulmonary stenosis.

In all hearts in which the origin of the orifices of the coronary arteries could be noted, they came from the aortic sinuses facing the pulmonary trunk irrespective of

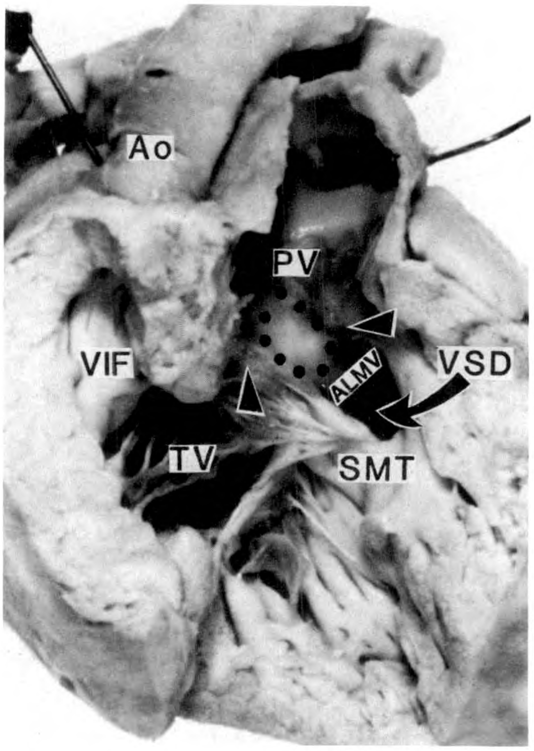

Fig 3. Specimen demonstrating fibrous continuity between the leaflets of the pulmonary valve and the mitral valve at the margins (arrowheads) *with a central muscular separation* (stippled margin)*.* (ALMV = *aortic leaflet of mitral valve;* Ao = *aorta;* SMT = *septomarginal trabeculation;* TV = *tricuspid valve;* VIF = *ventriculoinfundibular fold;* PV = *pulmonary valve;* VSD = *ventricular septal defect.)*

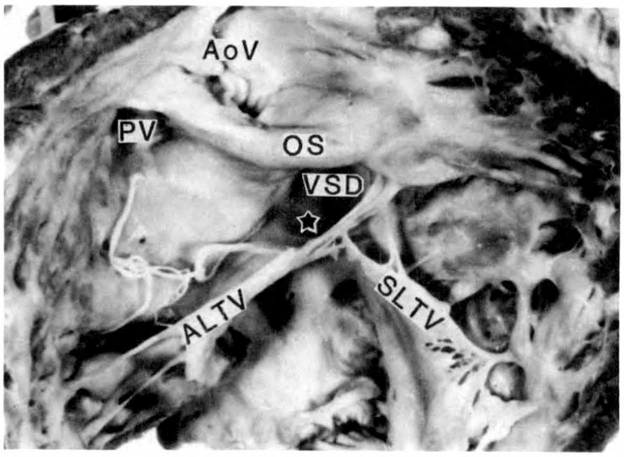

Fig 4. Specimen with double-outlet right ventricle, complete subaortic and subpulmonary muscular infundibulums, and a perimembranous ventricular septal defect. The asterisk indicates the fibrous posteroinferior margin of the defect produced by fibrous continuity between the leaflets of the mitral and tricuspid valves. (ALTV = *anterosuperior leaflet of tricuspid valve;* AoV = *aortic valve;* OS = *outlet septum;* PV = *pulmonary valve;* SLTV = *septal leaflet of tricuspid valve;* VSD = *ventricular septal defect.)*

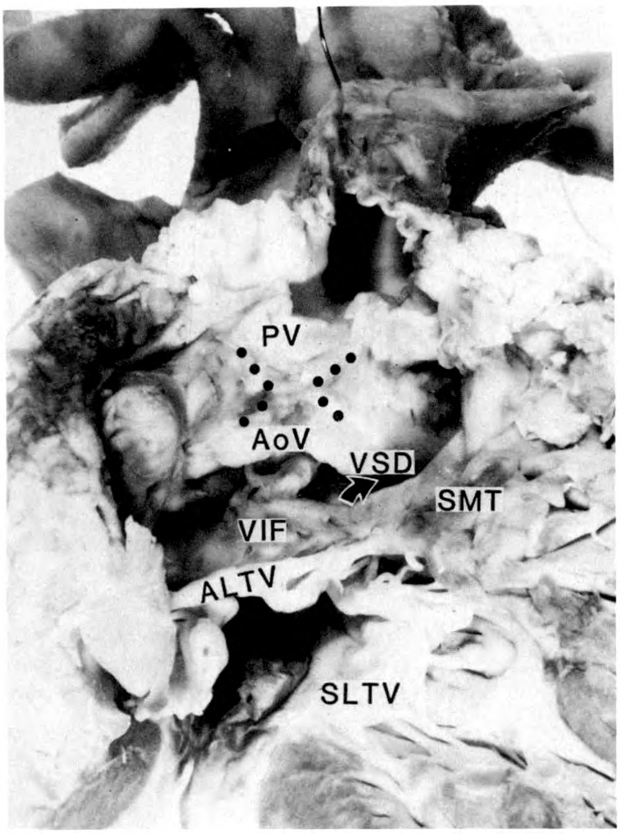

Fig 5. Specimen with double-outlet right ventricle, a ventricular septal defect that is subarterial and doubly committed but with a muscular posteroinferior rim, and fibrous continuity between the leaflets of the aortic and pulmonary valves (stippled margin). *(*ALTV = *anterosuperior leaflet of tricuspid valve;* AoV = *aortic valve;* PV = *pulmonary valve;* SLTV = *septal leaflet of tricuspid valve;* SMT = *septomarginal trabeculation;* VIF = *ventriculoinfundibular fold;* VSD = *ventricular septal defect.)*

truncal orientation. One heart had a single coronary artery that arose from the left-hand facing aortic sinus. No coronary artery took origin from the pulmonary trunk.

Measurement of subpulmonary and subaortic lengths yielded a subpulmonary to subaortic ratio of 0.91 ± 0.36 (n = 18; range, 0.42 to 1.56; median, 0.79). The ratio of the pulmonary to aortic circumference was 1.21 ± 0.72 (n = 20; range, 0.25 to 2.67; median, 1.12). Of 6 hearts that exhibited subpulmonary ventricular septal defects, and in which the great arteries were sufficiently intact to allow measurement, all had circumferential ratios greater than 1.0 (pulmonary trunk larger than aorta). Of 5 hearts with subaortic ventricular septal defects and great arteries suitable for measurement, all had circumferential ratios less than 1.0 (aorta larger than pulmonary trunk).

Comment

Despite restricting our selection of hearts studied to those having virtually exclusive connection of both great arteries to the cavity of the right ventricle, considerable variation was seen in the morphology of the fibrous skeleton and the orientation of the great arterial trunks. This was particularly marked with regard to the infundibular morphologies observed. In light of these findings, it seems too restrictive to maintain [6] that a heart must have both subaortic and subpulmonary infundibulums before it may be described as having double outlet from the morphologically right ventricle. Stringent application of this traditional criterion would have rendered almost two-thirds of this selection of hearts unclassifiable as double-outlet right ventricle despite the fact that both great arteries arose exclusively, as far as we could judge, from the right ventricle.

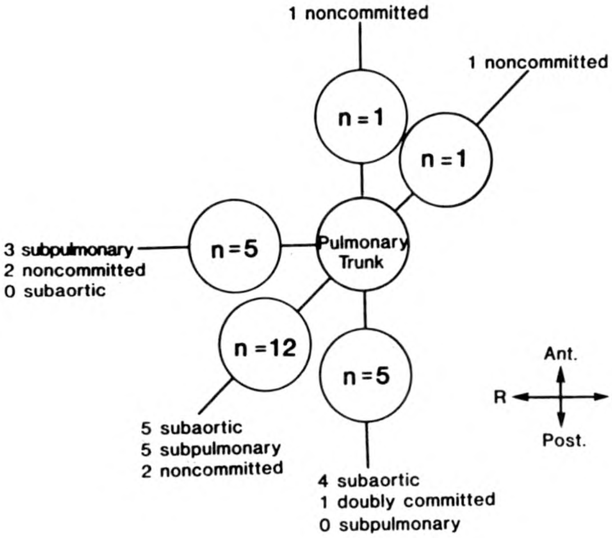

Fig 6. Schematic diagram of aortic positions in relation to the pulmonary trunk, with division of the types of ventricular septal defects found with each aortic position.

The origination of these "traditional" criteria has previously been brought into question by Bartelings [5], who noted the inconsistency between the early morphological descriptions of hearts with double-outlet right ventricle and studies that have subsequently employed the criterion of the bilateral infundibulum to define the entity. The landmark works of Neufeld and associates [9, 10], which provided some of the earliest detailed descriptions of hearts with double-outlet right ventricle, clearly established the existence of hearts with fibrous continuity between the leaflets of the aortic and mitral valves as a part of the spectrum of hearts with unequivocal connection of both great arteries to the right ventricle. As discussed by these authors, the co-existence of these two features resulted in elongation of the aortic leaflet of the mitral valve.

It appears that it was the detailed description of the so-called Taussig-Bing heart [11, 12], the original of which clearly possessed discrete subaortic and subpulmonary infundibulums (although the precise connection of the pulmonary trunk remained controversial [13]), that provided the impetus for the application of the features of the bilateral infundibulum to all hearts classified as double-outlet right ventricle. This criterion then received support from the radiographic studies of Baron [14] and Hallerman and co-workers [15], which put reliance upon separation of the leaflets of the mitral and aortic valves for the differentiation between tetralogy of Fallot and double outlet. This was despite, however, the reference by Baron [14] to the work of Neufeld and associates [10] that, as Bartelings [5] indicated, described a subgroup of hearts with double outlet that exhibited continuity between the leaflets of the aortic and mitral valves.

Presumably, the desire to retain the criterion of the bilateral infundibulum reflects a temptation to preserve nomenclature that refers to a specific morphological entity and that allows instantaneous and consistent recognition of that entity as well as its separation from others [6]. It is difficult now to find either morphological, clinical, or embryological bases for this approach. If used, confusion is the inexorable result. What name, then, is to be given to the hearts not possessing a bilateral infundibulum by using this approach? We should emphasize in this context that none of the hearts included within our present study showed the morphology of tetralogy of Fallot. Thus, our discussions concerning the significance of a bilateral infundibulum in the diagnosis of double-outlet right ventricle are peripheral, albeit important, to the ongoing debate concerning the distinction of the lesion from tetralogy of Fallot. It should also be noted in this context that no specimen had subpulmonary stenosis. This simply reflected the morphology of the hearts at our disposal.

The debate over "traditional" separations between hearts with double-outlet right ventricle and those with tetralogy of Fallot also has unclear foundations in light of the early report by Witham [16], the recognized initiator of the term double-outlet right ventricle. He grouped the hearts studied as those with "true persistent truncus," the "Eisenmenger type," and the "Fallot type"! Although he did not address valvar fibrous continuity as a morphological feature, he made a clinical and pathological distinction between the "Fallot type" of double-outlet right ventricle and hearts with tetralogy of Fallot that lack complete origin of the aorta from the right ventricle. This was primarily on the basis that the former displayed hypertrophy of both ventricles, rather than only of the right ventricle, as in the latter.

It must always be remembered that these earlier reports came in an era when diagnostic techniques were often insufficient to demonstrate all details of a given lesion, so that often it was necessary to make inferences. This is no longer the case. Currently, all pertinent features can now accurately be determined during life. In this light, we submit that clarity and consistency in description must account for all features of a malformed heart. Thus, "tetralogy of Fallot with double-outlet ventriculoarterial connection" becomes more descriptive and clinically relevant than simply "tetralogy of Fallot" when the greatest part of the aorta is connected to the right ventricle in a patient whose heart bears all the morphological features of tetralogy. Similarly, because of the well-recognized variability in location of the ventricular septal defect and its effect on clinical presentation, mere description of "double-outlet right ventricle" in the traditional sense now retains little value. Numerous surgical and morphological studies [1–4, 17, 18] have testified to the importance of characterization of the differences in these hearts in terms of the orientation of the great arteries and the type of ventricular septal defect (subaortic, subpulmonary, doubly committed, and noncommitted) for surgical decision-making and prognosis.

In this study, we have confirmed that, even when both arterial trunks are unequivocally connected to the right ventricle, there is marked inconsistency in the extent of obliteration of the muscular inner heart curvature ("absorption of the conoventricular flange") in producing continuity or discontinuity between the leaflets of the arterial and atrioventricular valves. This feature, therefore, has utility in morphological description but is unreliable as a criterion of morphological classification. As variations continue to be detailed, as in this and other studies, the need for less confusing and more descriptive terminology becomes more pronounced. Such efforts can be facilitated by using the term *double outlet* to describe a specific ventriculoarterial connection, to which it is suited, rather than to describe infundibular morphology, in which role it remains both confusing and counterproductive.

In terms of morphogenesis, the observed variations in arterial position and formation of the subarterial musculature support a role for the processes of absorption, rotation, and medial translocation of the ventricular outflow tracts. As observed by Van Mierop and Gessner [19] in studies of human embryos, there is leftward translocation of the outflow tracts during horizons 12 through 14 as described by Streeter [20, 21] (23 to 26 days gestational age). Over this period, there is a shift from an exclusive origin of the outlet component from the developing right ventricle to that producing an outlet in part from the left ventricle. This process occurs before the development of the swellings responsible for septation of the outflow tracts and the arterial pole. Then, as normal septation proceeds, the aortic orifice is in position to become connected with the developing outlet component of the left ventricle. A defect in the process of leftward shift would leave an exclusive connection to the right ventricle, or, if incomplete, predominant connection to the right ventricle. Further anomalous development in the process of septation could then produce the orientational variations of the great arteries as we have observed.

The more recent embryological studies of Bartelings and Gittenberger-de Groot [22] have shown that the process of septation of the ventricular outflow tract proceeds before that of truncal septation. The aortic orifice is already in close proximity to the superior atrioventricular cushion within the atrioventricular orifice, suggesting the minimal presence of a subaortic infundibulum in this area which must, effectively, be resorbed to produce valvar continuity. As regression of the muscular inner heart curvature proceeds in the normal and abnormal heart, and based on precedent normal or abnormal translocation or septation, our observed variations in the fibrous skeleton suggest that it is the orifice of the arterial trunk initially in closest proximity to the superior atrioventricular endocardial cushion that achieves fibrous continuity with the atrioventricular valve(s). And, as the variations suggest, the irregularity of this regressive process produces a spectrum, in these selected hearts, from complete discontinuity to extensive areas of valvar continuity, with intermediate forms that include muscular remnants of the inner curve within those areas of fibrous continuity (see Fig 3). Experiments with irradiation of mammalian embryos by Okamoto and associates [23] have shown that development of the ventricular outflow tracts is a complex process dependent on the formation of the cardiac loop; the volume and length of the trunks; the arrangement of the valvar cushions and outflow ridges; and the position, amount, and timing of appearance and disappearance of focuses of cell death within the ridges. Recognition of the many variables involved should presage the expectation of the broad variations in pathology that have been historically observed.

Although our sample of specimens was small and selected, we feel justified in making other inferences from our findings. From the relationships between aortic position and type of defect it appears that, in the presence of a right aorta (in side-by-side orientation), the finding of a subaortic defect would be unlikely, and similarly, in the presence of a posteriorly positioned aorta, a subpulmonary defect would be unlikely.

Measurements of the components of the outlet septum revealed virtual comparability in subaortic and subpulmonary lengths. Such a relationship was also alluded to in the reports by Neufeld and associates [9, 10] and Witham [16], with their observations that the distinguishing feature between hearts having tetralogy of Fallot and those with origin of both great vessels from the right ventricle was that in the latter, "both semilunar valves are in the same cross-sectional and coronal body planes" [9]. This is a finding that contrasts with those in our recent study of hearts with tetralogy of Fallot [8]. In the latter hearts, using similar measurements, we noted a mean ratio of subpulmonary to subaortic lengths of 1.54 ± 0.41. The mean of 0.91 ± 0.36 obtained in this selection of hearts gives a difference that is statistically significant from that obtained in the hearts with tetralogy (Student's *t* test, $p < 0.001$). Another finding in the embryologic study of Bartelings and Gittenberger-de Groot [22], correlating with their observation that the aortic orifice achieved proximity to the atrioventricular orifice concomitant with the beginnings of septation of the outflow tract but before that of truncal septation, was that this preexisting proximity produced a longer subpulmonary than subaortic length in the outlet septum. It is the infundibular morphology, therefore, that determines the existence of tetralogy of Fallot, even when both arterial trunks spring almost exclusively from the right ventricle.

Due to the minute dimensions of the outlet septum in the mature heart, comparisons between hearts with tetralogy and normal hearts are difficult, if not impossible. The differential ratios, nonetheless, suggest differing temporal relationships in the defects producing hearts with unequivocal double-outlet right ventricle in the absence of tetralogy as opposed to those with the morphology of tetralogy. This supports the suggestion by Van Mierop and Gessner [19] that the basic defect in double outlet is at the stage of leftward shift of the outflow tract before septation and its attendant development of a shorter subaortic infundibular length. The differential in length found in hearts with tetralogy then supports the suppositions by Goor and co-workers [24] and Becker and colleagues [3] that the morphogenesis of tetralogy is due to anomalous septation and "inversion," steps that occur subsequent to the leftward shift of the outflow tracts and, according to the work by Bartelings and Gittenberger-de Groot [22], also subsequent to the establishment of the differential subarterial lengths as in normal embryos. The finding in this study of a larger circumference of the great vessel to which the ventricular septal defect was committed may also be of developmental importance. This, too, reflects the early stage of development in which the overall anomaly is produced. It supports the importance of hemodynamic factors in growth of the great vessels, because the committed vessel would receive the majority of the outflow from both ventricles.

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Progress of Patients With Pulmonary Atresia After Systemic to Pulmonary Arterial Shunts

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Between February 1980 and June 1987, 42 shunts were placed in 39 infants with pulmonary atresia: 33 were modified Blalock-Taussig shunts with polytetrafluoroethylene (PTFE) and 9 were classic Blalock-Taussig shunts. There were four hospital deaths not related to the shunts. The remaining 35 patients were followed up for 1.6 months to 6.3 years (mean, 24.7 ± 18 months). Repeat cineangiocardiographic studies revealed stenosis or distortion of the pulmonary arteries related to the site of the shunt in 11/22 patients (50%) with PTFE shunts and in 1/6 (17%) with classic Blalock-Taussig shunts; the stenosis was severe in only 1 patient. Mean increase in the pulmonary arterial index in the group with classic Blalock-Taussig shunts was 117 ± 52 mm^2/m^2 (not significant) and in the group with PTFE shunts, 158 ± 21 mm^2/m^2 ($p < 0.001$). Late shunt occlusion occurred in 1 patient 23 months postoperatively. Thereafter, shunt patency rate remained at 94% ± 6%. At the end of 1 year 81% ± 7% of patients were judged to have adequate palliation, but between 2 and 3 years, only 60% ± 10%. Univariate analysis showed that after 2 years the ranking order for successful palliation was classic Blalock-Taussig, 5-mm PTFE, and 4-mm PTFE shunts, but differences did not achieve statistical significance.

(Ann Thorac Surg 1991;51:401–7)

The long-term prognosis for patients with pulmonary atresia has improved since the introduction of the Fontan-type procedure and advancements in staged repair [1, 2]. Most patients with pulmonary atresia require a palliative shunt soon after birth for survival. For most of the period of this study, the objective of a neonatal shunt was palliation for something approaching 4 years for those requiring a Fontan-type repair [3] and for as long as practical for those requiring a right ventricular outflow conduit. The aim of this study was to determine the adequacy and duration of palliation in patients with pulmonary atresia who received systemic to pulmonary arterial shunts.

Patients and Methods

All infants with pulmonary atresia who received systemic to pulmonary arterial shunts between February 1980 and June 1987 were included in this study. Forty-two shunts were placed in 37 infants with pulmonary atresia and in 2 with near pulmonary atresia (one with extreme pulmonary stenosis and suprasystemic pressure in a hypoplastic right ventricle and the second with extreme pulmonary stenosis and complex associated defects). The age of the patients at the initial shunt procedure ranged from 1 to 380 days (average, 34.7 days; median, 4 days) (Table 1). The patients were subdivided into three diagnostic groups: (1) pulmonary atresia of the tetralogy of Fallot type (PA + VSD), (2) pulmonary atresia with an intact ventricular septum (PA + IVS), and (3) pulmonary atresia associated with complex cardiac anomalies (PA + complex) (Tables 1, 2). The patients attended the clinic at regular intervals and the end of the study follow-up was June 30, 1989.

Preoperatively, prostaglandin E_1 was given in 63% of the patients to maintain ductal patency and was discontinued after the operation. Heparin, 1 mg/kg, has been used intraoperatively since 1982 and was usually not reversed with protamine. None of the patients received antiplatelet therapy postoperatively.

The decision about the type and size of shunt was made by the surgeon at the time of the operation. Sixteen patients received 4-mm-diameter polytetrafluoroethylene (PTFE) tube grafts and 14 received 5-mm grafts. In 27 patients the PTFE shunt was anastomosed from the subclavian to the ipsilateral pulmonary artery, in 2 patients to the main pulmonary artery, and in 1 patient from the upper descending thoracic aorta to the left pulmonary artery. Nine of the patients had classic Blalock-Taussig shunts initially. The diameter of the ipsilateral pulmonary artery measured on the preoperative cineangiocardiogram in patients receiving 4-mm PTFE shunts was 3.6 ± 0.5 mm, whereas in patients receiving 5-mm PTFE shunts the diameter was 4.2 ± 1.1 mm ($p = 0.05$), and in those receiving classic Blalock-Taussig shunts the diameter was 4.1 ± 0.8 mm ($p = 0.05$).

Three patients required early repeat shunts in the first postoperative day: two thrombosed 4-mm PTFE shunts were replaced with another 4-mm or 5-mm shunt and one probably kinked Blalock-Taussig shunt was replaced with a 5-mm PTFE shunt. In each case the second operation

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Table 1. *Age of Patients at Initial Shunt Procedure*

Age at Initial Shunt Procedure	Pulmonary Atresia Diagnostic Group			Total
	PA + VSD	PA + IVS	PA + Complex	
<1 wk	9	11	3	23 (59%)
1 wk to 1 mo	3	3	2	8 (20%)
1 mo to 3 mo	2	3	0	5 (13%)
3 mo to 1 y	2	0	1	3 (8%)
Total	16	17	6	39

IVS = intact ventricular septum; PA = pulmonary atresia; VSD = with ventricular septal defect, tetralogy of Fallot type of pulmonary atresia.

provides the basis for the follow-up in this presentation (see Table 2).

At the time of the initial PTFE shunt, additional procedures included ten pulmonary valvotomies and one insertion of a right ventricular outflow patch in patients with PA + IVS. At the time of operation the coronary circulation did not appear dependent on flow from the right ventricle through fistulous connections in any of these patients. Six of these plus 2 others with PA + IVS and 1 with PA + VSD had ligation of the patent ductus arteriosus. No patient with a classic Blalock-Taussig shunt had a pulmonary valvotomy or enlargement of the right ventricular outflow tract.

Preoperative cardiac catheterization and cineangiocardiography were performed in 37 of the 39 patients. Two patients with tetralogy type of pulmonary atresia had shunts on the basis of the echocardiographic findings only. Postoperative cardiac catheterization studies were performed in 28 patients. The interval between the preoperative and postoperative studies ranged from 37 days to 54 months (average, 22 months).

Cineangiocardiograms were reviewed to assess shunt patency or stenosis, and growth or distortion of the pulmonary arteries. From biplane, oblique views the diameters of the right and left pulmonary arteries were measured proximal to the upper lobe branch. The measured diameters were converted to true measurements by comparison with the known diameter of the cardiac catheter and with a 1-cm grid filmed with each cineangiogram. A pulmonary artery index was calculated by a method similar to that of Nakata and associates [4]: the sum of the cross-sectional areas of right and left pulmonary arteries was divided by the body surface area.

Thirteen autopsy specimens were available for review regarding shunt patency and site of obstruction.

Univariate analysis was used to assess the importance of the diagnostic group or the size of the PTFE shunt on the adequacy of palliation. Student's paired t test was used in the assessment of pulmonary growth. The duration of adequate palliation was determined by the Kaplan-Meier survival analysis. Palliation was defined as inadequate when a further shunt or nonelective repair was required even if the shunt was patent. Withdrawal endpoints included last clinical follow-up, elective repair, or death not related to shunt adequacy.

Table 2. *Types of Shunt*

Diagnostic Group	PTFE Graft		Classic Blalock-Taussig	Total
	4 mm	5 mm		
PA + VSD	5	8	3	16
PA + IVS	8	7	2	17
PA + Complex	2	1	3	6
Total	15 (38%)	16 (41%)	8 (21%)	39

IVS = intact ventricular septum; PA = pulmonary atresia; PTFE = polytetrafluoroethylene; VSD = ventricular septal defect, tetralogy of Fallot type of pulmonary atresia.

Results

No intraoperative deaths occurred with the initial shunts. Four patients with PA + IVS died during hospitalization (Table 3). The shunts were patent at postmortem examination.

The remaining 35 patients were followed for 1.6 (early death) to 76 months (mean, 25 ± 18 months). Nine patients died after discharge; two deaths were due to failed shunts (Table 3, Fig 1). Five patients with PA + IVS had right ventricular to coronary artery fistulous connections [5]. Two died of a myocardial infarction, and coronary arterial abnormalities probably contributed to the deaths of 2 others who died suddenly but did not have postmortem examinations (see Table 3).

Five patients required repeat shunt procedures after 5 to 23 months (average, 14 months). Five patients have had nonelective repairs, 14 have had elective repairs, and 7 are awaiting surgical repair.

Shunt Patency, Stenosis, and Adequacy of Palliation

Two 4-mm PTFE shunts were completely occluded with thrombus on the first postoperative day and, as already described, new shunts were placed. The pulmonary arterial end of a 5-mm PTFE shunt was occluded by thrombus 23 months after insertion (see Fig 1a). There were no further shunt occlusions beyond this time (Fig 2). In 1 patient the proximal subclavian artery was occluded but the shunt filled by collaterals.

Stenosis of the shunt was found on cineangiocardiograms in 12/21 (57%) PTFE shunts and 5/7 (71%) classic Blalock-Taussig shunts, and was confirmed at autopsy in 2 of these patients. Stenosis was also demonstrated at autopsy in 2 further patients who had not undergone cineangiography. The sites of late stenosis are listed in Table 4. Important narrowings were at least as common in 5-mm PTFE grafts as in 4-mm PTFE grafts.

Cumulative probabilities of adequacy of palliation are depicted for the total number and for the various types of shunts in Figures 3 to 5. Palliation was adequate in 81% ± 7% after 1 year but in only 66% ± 9% at 2 years and 60% ± 10% after 3 years (see Fig 3). Palliation appeared similar in patients with 4-mm or 5-mm PTFE shunts during the first year but late inadequacy was more common in the

Table 3. Causes of Death

Diagnostic Group	Type of Shunt	Interval to Death	Cause of Death	Postmortem Examination
Hospital deaths				
PA + IVS[a]	4 mm	4.5 h	Damage to branch of single cor art with ventriculotomy	Yes[b]
PA + IVS[a]	4.5 mm	1 d	Tri regurg, low CO	Yes[b]
PA + IVS[a]	5 mm	1 d	Cerebral AV fistula with hemorrhage	Yes[b]
PA + IVS[a]	4 mm	2 d	Renal vein thrombosis	Yes[b]
Late Deaths				
PA + VSD	5 mm	23 mo	Failed shunt—occluded	Yes
PA + IVS[a]	5 mm	5 mo	Failed shunt—narrowed	Yes[b]
PA + IVS[a]	BT	3 mo	Myocardial infarction	Yes[b]
PA + IVS[a]	5 mm	14 mo	Myocardial infarction	No
PA + IVS[a]	4 mm	2.5 mo	Probable myocardial damage	No
PA + IVS[a]	5 mm	10 mo	Probable myocardial damage	No
PA + Complex	4 mm	23 mo	Unknown	No
PA + VSD	4 mm	29 mo	Cerebrovascular accident	No
PA + IVS	BT	3.5 y	Bacterial endocarditis	Yes[b]

[a] Right ventricular to coronary arterial fistulous connections. [b] Shunt patent at postmortem.

AV = arteriovenous; BT = Blalock-Taussig; CO = cardiac output; cor art = coronary artery; IVS = intact ventricular septum; PA = pulmonary atresia; regurg = regurgitation; Tri = tricuspid valve; VSD = ventricular septal defect, tetralogy of Fallot type of pulmonary atresia.

patients with 4-mm PTFE shunts thereafter (not significant [NS]; see Fig 4). Adequacy of palliation was better for the patients with the classic Blalock-Taussig shunts after 2 years (NS). No statistically significant difference was found between the diagnostic groups (see Fig 5).

Pulmonary Arterial Distortion or Growth

Mild narrowing or stenosis in the interconnections between right and left pulmonary arteries was present in 27 patients preoperatively (7 with PA + VSD, 17 with PA + IVS, 3 with PA + complex). This progressed to moderate narrowing in 7 patients after shunt placement (4 with PA + VSD, 3 with PA + IVS). Moderate preoperative narrowing persisted in 5 patients (3 with PA + VSD and 2 with PA + complex).

Distortion or stenosis of the pulmonary artery related to the site of the shunt was found in 12 of the 28 patients (43%) who had postoperative cineangiograms: 11/21 (52%) with PTFE shunts (4 patients with 5-mm PTFE shunts and 7 patients with 4-mm PTFE shunts) and 1/7 (14%) with classic Blalock-Taussig shunts. The stenosis was mild or moderate in 11 of the arteries and was present preoperatively in 4 (1 with PA + VSD, 3 with PA + complex). Severe stenosis was found in 1 patient whose shunt had been placed into the right upper lobe branch. The stenosis was present in 6/16 patients with PA + VSD compared with 3/17 with PA + IVS (NS) and 3/6 with PA + complex.

Pulmonary arterial growth was assessed in 25 of the 26 patients with repeat cineangiograms. Two patients had small pulmonary collaterals (Fig 6). Two patients who had large pulmonary collaterals to their right lungs are not included in the assessment regarding pulmonary arterial growth. One was excluded because the size of the right pulmonary artery could not be accurately measured; the other has not had a repeat study. In the 6 patients who received classic Blalock-Taussig shunts the pulmonary arterial index increased from 106 ± 66 to 223 ± 133 mm^2/m^2 (NS), in 10 patients with 5-mm PTFE shunts the index increased from 149 ± 73 to 325 ± 152 mm^2/m^2, and in 9 patients with 4-mm PTFE shunts the index increased from 141 ± 35 to 280 ± 88 mm^2/m^2 ($p < 0.002$; see Fig 6). In 10 patients with PA + VSD the pulmonary arterial index increased from 109 ± 39 to 220 ± 98 mm^2/m^2; in 9 patients with PA + IVS the index increased from 145 ± 78 to 309 ± 145 mm^2/m^2 and in 6 patients with PA + complex the index increased from 167 ± 47 to 356 ± 114 mm^2/m^2. The differences between the three clinical groups were not statistically significant. Previously published values for the normal index are 330 ± 30 mm^2/m^2 [4] and 351 ± 64 mm^2/m^2 in younger patients [6].

Comment

The emphasis of this study has been to assess the adequacy of palliation in infants with pulmonary atresia after systemic to pulmonary shunts. Aside from complete occlusion, any criteria used to define adequacy of palliation given by the shunt remain difficult. The type of shunt did not appear to significantly affect the frequency of heart failure, which occurred in 3/14 patients (21%) with 5-mm PTFE shunts, in 2/13 (15%) with 4-mm PTFE shunts, and in 1/8 (12.5%) with classic Blalock-Taussig

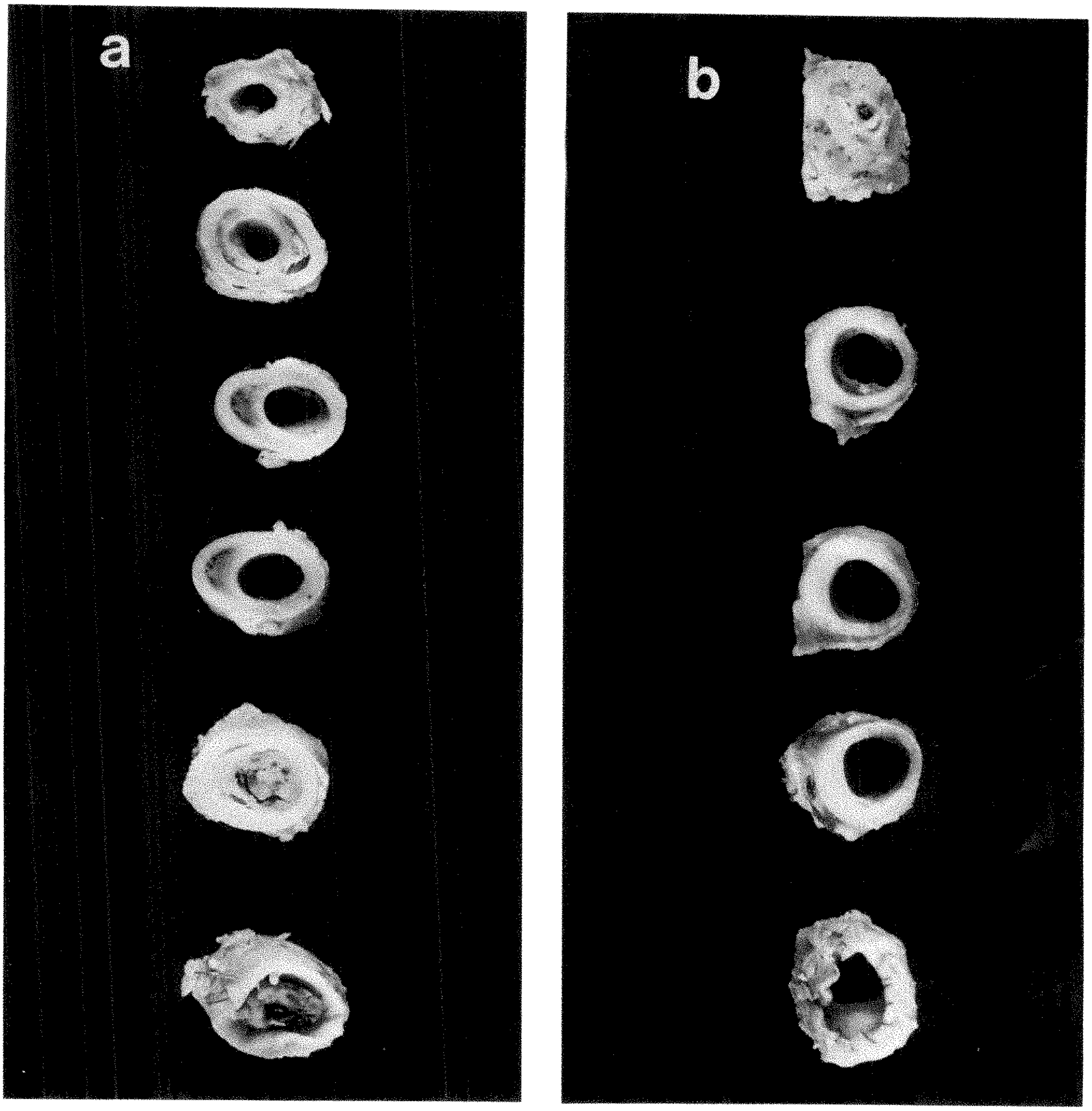


Fig 1. Polytetrafluoroethylene tube grafts from the 2 patients who died of shunt failure. The 5-mm grafts are sectioned transversely from the subclavian arterial anastomosis (upper sections) to the pulmonary arterial anastomosis (lower sections). In (a) the lumen is eccentrically narrowed by pseudointima and recanalized. The pulmonary arterial end is occluded by thrombus. In (b) the subclavian anastomosis is small; the lumen is minimally narrowed by pseudointima.

shunts. The time when the patient needs further intervention is subjective. A number of patients in this study failed to meet the criteria of adequate palliation because of increasing cyanosis, poor weight gain, and frequent respiratory infections requiring early physiologic repair even though the shunts were clinically patent.

Thirty-seven of our patients had pulmonary atresia and 2 had extreme stenosis, effectively atresia. The rates of shunt patency and adequacy of shunts are similar to other series that include a higher proportion of patients with pulmonary stenosis [7–16]. Several studies suggest that the PTFE shunt may be the most effective method in infants in terms of duration of palliation and patency [10, 12–14]. In our study, there has been only one instance of late occlusion of a PTFE shunt. However, using our criteria only 60% of our patients were considered to have satisfactory palliation at 3 years. Clearly deterioration in shunt function may be disguised when there is substantial

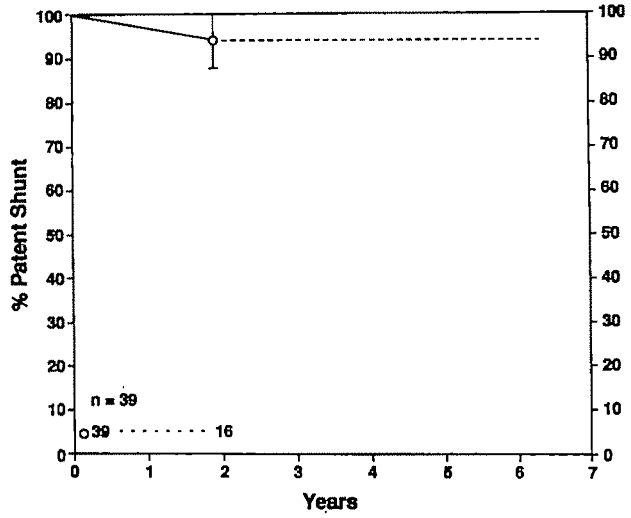


Fig 2. Actuarial curve depicting the percentage of patency of the shunts on follow-up against the years postoperatively. (The two shunts occluded on the first day, patients undergoing reoperation, are not included.)

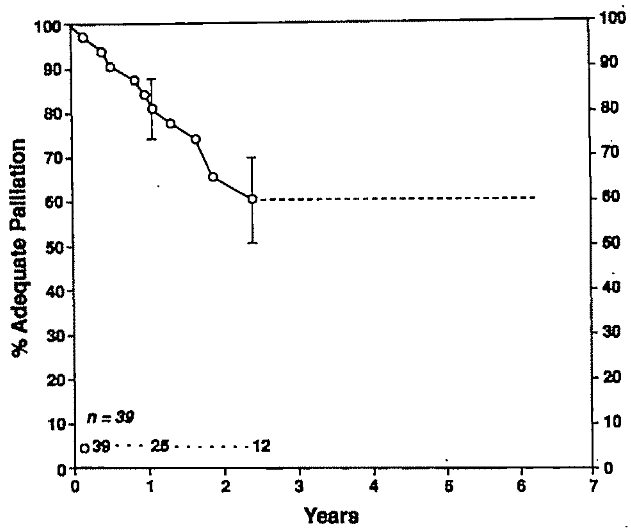


Fig 3. Actuarial curve showing the percentage with adequate palliation after placement of the shunts for the total group. (Dotted lines *indicate that either the number has fallen below 10 or there have been no further incidents.)*

flow through the normal pathway as with tetralogy of Fallot and tricuspid atresia. Fewer than 40% of patients in previous series have had pulmonary atresia, and conclusions from those studies cannot be compared directly with conclusions regarding patients who are totally shunt dependent. In our group pulmonary valvotomy probably contributed to substantial forward flow in 2 patients (see Fig 6) and collaterals to one lung contributed in 2 others. All 4 had satisfactory shunts. All other patients were totally or mainly shunt dependent.

Stenosis of PTFE shunts may occur at the proximal or distal anastomosis or along the length of the graft (see Table 4, Fig 1). Early shunt occlusion is likely related to thrombosis [10, 13, 15, 17]. Postoperative use of antiplatelet therapy is probably indicated [9, 11, 16] but was not used in this series. Stenosis of the shunt may increase with progressive narrowing of the lumen by pseudointimal proliferation [7, 9, 17] or be due to narrowing of the proximal anastomosis [7, 15] or of the subclavian artery proximal to the shunt [11].

It is noteworthy that 32/37 of our patients showed some narrowing of the interconnections of the pulmonary arterial branches preoperatively, and this increased postoperatively in 7. The prevalence of postoperative distortion of the pulmonary arteries in our series (12/28 cases studied by cineangiography) was similar to that reported by Ullom and co-workers [14]. In at least 4 of our patients, the stenosis almost certainly represented progression of a

Table 4. Late Stenosis in 19 Shunts

Variable	PTFE Shunt[a] 4 mm	PTFE Shunt[a] 5 mm	Blalock-Taussig
No. of shunts	15	16	8
No. obstructed	5	8	6
Site of stenosis			
Subclavian artery (proximal)	1	2	. . .
Proximal anastomosis	2	4	. . .
Distal anastomosis	2	2	6[b]
Length of graft	2	5	. . .

[a] More than one site of stenosis was present in 6 patients. [b] Mild stenosis in 3, moderate in 3.

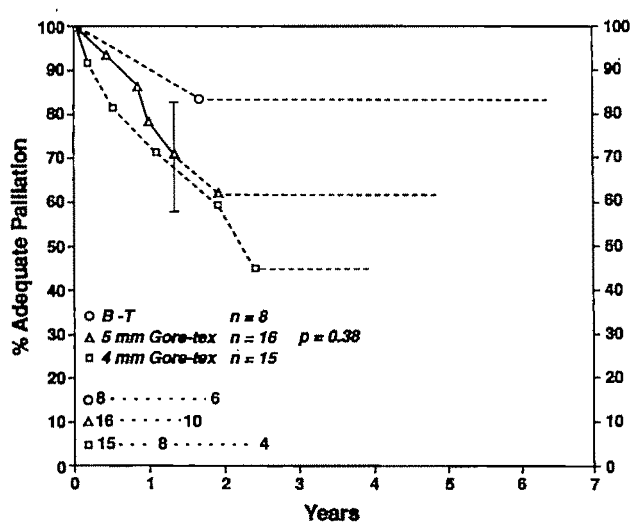


Fig 4. Actuarial curve comparing the percentage with adequate palliation in patients with different types of shunts. (BT = classic Blalock-Taussig shunt; Gore-Tex = *polytetrafluoroethylene shunts;* p = *0.38 indicates that the differences between the groups are not significant;* dotted lines *indicate that either the number has fallen below 10 or there have been no further incidents.)*

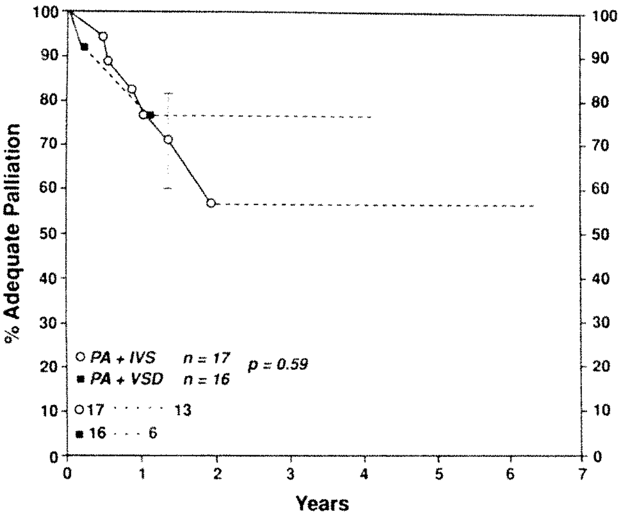


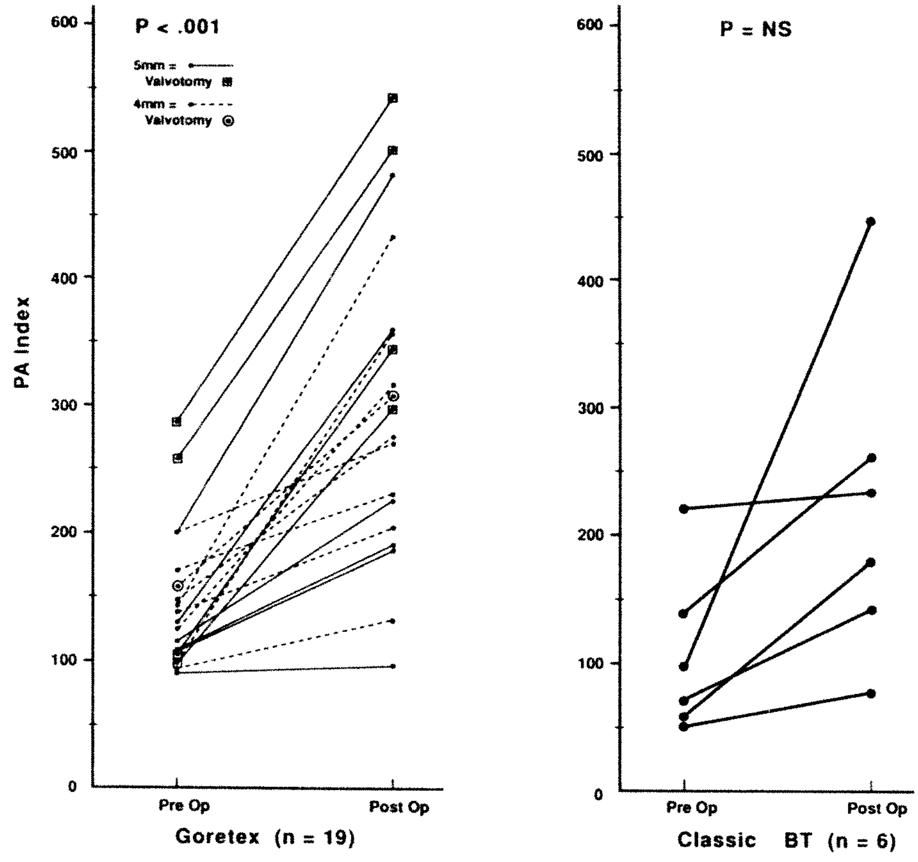
*Fig 5. Actuarial curve comparing the percentage with adequate palliation in patients with tetralogy type of pulmonary atresia (*PA + VSD*) and those with an intact ventricular septum (*PA + IVS*). (*p = 0.59 *indicates that the difference between the groups is not significant;* dotted lines *indicate that either the number has fallen below 10 or there have been no further incidents.)*

preoperative anomaly, and this was also possible in a number of others. In only 1 patient was the distortion severe, and that affected only the right upper lobe. Narrowing or distortion did not affect subsequent management plans in any patient, but mild or moderate abnormalities could well affect postoperative progress, especially after a Fontan-type procedure. Severe distortion has been reported [13], but some authors reported no distortion or narrowing related to the shunt [7, 11, 15]. In each case, this question was peripheral to the main discussion and it seems likely that it received limited attention.

Several studies have reported better palliation with 5-mm rather than 4-mm PTFE grafts [7, 11, 16], and our results are compatible with this. We have no evidence in this study that the size of the graft affected long-term left ventricular or pulmonary vascular resistance and have tended to favor the larger shunt when practical. With the trend toward earlier second-stage procedures, however, emphasis is shifting toward the procedure that seems least likely to distort the pulmonary arteries.

In summary, the PTFE shunt was associated with a low incidence of occlusion. By 2 years, however, palliation was considered adequate in only two-thirds of our patients. We now recommend restudy to check changes in the shunt and pulmonary arteries before 2 years. There was no evidence that the choice of shunt affected long-term left ventricular function, pulmonary arterial distortion, or resistance, but these factors must be considered along with the duration of adequate palliation in planning the first procedure in infancy.

*Fig 6. The increase in pulmonary arterial index (*PA index*) measured from cineangiocardiograms obtained preoperatively (*Pre Op*) and postoperatively (*Post Op*) in patients who received Gore-Tex or classic Blalock-Taussig (*BT*) shunts. The mean increase for the PTFE shunts = 158 ± 21 mm²/m² and for the classic Blalock-Taussig shunts = 117 ± 52 mm²/m². The smallest PA index in each group was seen in the 2 patients with small pulmonary collaterals. The largest PA indices were seen in 2 of the patients who had a pulmonary valvotomy in addition to the Gore-Tex shunt.*



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Superiority of Retrograde Cardioplegia After Acute Coronary Occlusion

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Because antegrade cardioplegia may limit the distribution of cardioplegia beyond a coronary occlusion, this study was undertaken to determine whether retrograde coronary sinus cardioplegia provides superior myocardial protection during revascularization of an acute coronary occlusion. In 20 adult pigs, the second and third diagonal branches were occluded with a snare for 1½ hours. Animals were then placed on cardiopulmonary bypass and underwent 30 minutes of ischemic arrest with multidose, potassium, crystalloid cardioplegia. In 10 animals, the cardioplegia was given antegrade through the aortic root, whereas in 10 others, it was given retrograde through the coronary sinus. After the arrest period, the coronary snares were released and all hearts were reperfused for 3 hours. Postischemic damage in the myocardium beyond the occlusions was assessed by wall motion scores using two-dimensional echocardiography (4 = normal to −1 = dyskinesia), the change in myocardial pH from preischemia, and the area of necrosis/area of risk (histochemical staining). Hearts protected with retrograde coronary sinus cardioplegia had less tissue acidosis (change in pH = 0.08 ± 0.03 versus 0.41 ± 0.13; $p < 0.05$), higher wall motion scores (2.0 ± 0.6 versus 1.3 ± 0.3; not significant), and less myocardial necrosis (43.4% ± 3.6% versus 73.3% ± 3.5%; $p < 0.0001$). We conclude that retrograde coronary sinus cardioplegia provides more optimal myocardial protection than is possible with antegrade cardioplegia after revascularization of an acute coronary occlusion.

(Ann Thorac Surg 1991;51:408–12)

The presence of coronary occlusions can alter the distribution of antegrade cardioplegia [1]. This can lead to myocardial injury and depressed postoperative left ventricular function. Experimental studies have shown that in the presence of coronary occlusions, retrograde cardioplegia results in better myocardial cooling and more complete recovery of function in the area of the myocardium beyond the occlusions [2–4]. Nevertheless, recent clinical studies in patients undergoing coronary artery bypass grafting have shown that retrograde cardioplegia appears to offer no additional myocardial protection as compared with antegrade techniques [5, 6]. In these studies, patients had normal ventricular function and stable angina patterns. A more accurate assessment of the potential advantages of retrograde cardioplegia would be in the setting of acute coronary ischemia such as that which occurs after a failed balloon angioplasty.

Attempts to assess the clinical efficacy of a cardioplegia technique after emergent coronary artery bypass grafting are always difficult because of persistent postoperative wall motion changes, which may be independent of the degree of protection and the relative insensitivity of enzyme levels and scanning techniques. Histochemical staining techniques in the area of risk may be a more sensitive variable to judge the benefits of a cardioplegic technique used for revascularization of acutely ischemic myocardium [7, 8]. This experimental study was therefore undertaken to determine whether retrograde coronary sinus cardioplegia would result in more optimal myocardial protection than antegrade cardioplegia after an acute coronary occlusion in a setting analogous to a failed percutaneous transluminal coronary angioplasty. In addition to determining the recovery of regional wall motion function, this study also attempted to determine whether retrograde cardioplegia might decrease the extent of myocardial necrosis using histochemical staining techniques.

Material and Methods

Preparation

Twenty adult pigs (26 to 32 kg) were premedicated with intramuscular morphine sulfate (2 mg/kg), anesthetized with α-chloralose (75 mg/kg), and placed on positive-pressure endotracheal ventilation. A median sternotomy was performed and catheters were placed into the aorta and femoral vein for monitoring systemic pressure and administering fluids. The azygos vein was ligated and the animals were heparinized (3 mg/kg). The second and third diagonal branches were then occluded with snares just distal to the takeoff of the left anterior descending coronary artery for 90 minutes. All animals were then placed on total cardiopulmonary bypass (Sarns Membrane Oxygenator; Sarns, Inc, Ann Arbor, MI) with a No. 20 cannula in the femoral artery (C.R. Bard, Inc, Billerica, MA) and a No. 36 venous return catheter (Sarns) in the right atrium. A catheter was inserted into the left atrium

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to infuse volume so that left ventricular end-diastolic pressure could be varied. Mean arterial blood pressure during cardiopulmonary bypass ranged from 65 to 75 mm Hg and pump flow was kept at 80 mL · kg^{-1} · min^{-1}. The hematocrit averaged 0.26 ± 0.02 and pH was maintained at 7.43 ± 0.03.

After the institution of cardiopulmonary bypass, all hearts underwent 30 minutes of cardioplegic arrest. After this arrest period, the cross-clamp was removed, the coronary snares were released, and all hearts were reperfused on cardiopulmonary bypass at 37°C for 3 hours.

Measurements and Data Analysis

Electrocardiographic leads were placed to measure heart rate and to monitor electrical activity during arrest. Left ventricular end-diastolic pressure was recorded with a piezoelectric Mikro-Tip catheter pressure transducer (Millar Instruments, Inc, Houston, TX) inserted through a stab wound in the left ventricular apex. Systemic body temperature was measured with a rectal temperature probe (Yellow Springs Instrument Co, Yellow Springs, CO). Myocardial tissue pH was measured with a pH probe (Khuri Tissue Ischemia Monitor; Vascular Technology Inc, North Chelmsford, MA) and was standardized according to myocardial temperature, which was measured simultaneously with a temperature probe (Vascular Technology). Temperature and pH were measured in the center of the area of risk between the second and third diagonal vessels and in the unobstructed circumflex coronary artery distribution. Control pH measurements were made after a 30-minute period of equilibration and then recorded on-line along with myocardial temperature during the periods of coronary occlusion, cardioplegic arrest, and reperfusion. The pH values were expressed in absolute numbers and as the change in pH from preischemia. The pH and change in pH were recorded for each experiment and then averaged for all experiments in the antegrade cardioplegia and retrograde cardioplegia groups. Similarly, myocardial temperature in the area at risk and circumflex distribution was averaged during cardioplegic arrest and averaged for each cardioplegic group.

Two-dimensional echocardiograms were obtained with a hand-held 3.5-MHz ultrasound transducer (ATL, Temple, AZ). Left ventricular end-diastolic volume was obtained by planimetry of a perpendicular long-axis length and a short-axis area as previously described [9]. The same echocardiographic short-axis sections were also used to assess wall motion changes. The ventricle was arbitrarily divided into eight anatomical areas and wall motion was analyzed qualitatively by a numerical score in which 4 = normal, 3 = mild hypokinesis, 2 = moderate hypokinesis, 1 = severe hypokinesis, 0 = akinesis, and −1 = dyskinesis. Echocardiographic sections for wall motion analysis were obtained as left ventricular end-diastolic pressure was varied using the right heart bypass technique at a constant afterload (mean atrial pressure = 65 mm Hg). Only sections with the same left ventricular end-diastolic volume during the preischemic, coronary occlusion, and reperfusion periods were used for analysis so that preload conditions were similar. Measurements were made in a double-blind fashion by an experienced echocardiographer (S.B.) and were averaged for the periods of coronary occlusion and reperfusion for each experiment and, in turn, for both the antegrade and retrograde cardioplegia groups.

The area of risk and area of necrosis were determined by histochemical staining techniques as previously described [7, 8]. After the 3-hour reperfusion period, the second and third diagonal branches were reoccluded, the ascending aorta was cross-clamped, and the area of risk was determined by injecting 60 mL of phthalo-blue dye (Harshaw-Filtrol, Cleveland, OH) into the aortic root through a 9F catheter. The left ventricle was then excised and cut into 5- to 10-mm cross-sectional slices. The infarct area was determined by incubating the slices in triphenyltetrazolium chloride (Sigma Chemical Co, St. Louis, MO) for 30 minutes and then placing them in formaldehyde overnight. The next morning, the stained slices were placed under a glass plate and traced on clear plastic sheets. With reperfusion of ischemic myocardium there is washout from the nonviable cells of dehydrogenases necessary to reduce nitro blue tetrazolium, and these areas remain pale [7]. The areas of risk and infarct were then measured by planimeter for each slice to obtain the area of risk compared with the total left ventricular mass, and the percent area of infarct in that area of risk.

Statistical evaluation between the antegrade and retrograde cardioplegic groups was done with nonpaired *t* tests. All data were expressed as the mean ± standard error. Data were considered significant at the *p* less than 0.05 level.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Experimental Groups and Protocols

After the institution of cardiopulmonary bypass, all animals were systematically cooled to 28°C and the aorta was cross-clamped for 30 minutes with the diagonal vessels occluded. Hearts were protected with cold (4°C) crystalloid (D2.5 .45 NS) potassium (25 mEq/L) cardioplegia (HCO_3, 5 mEq/L; pH, 7.55; 290 mosm) supplemented with topical hypothermia. The initial cardioplegia dose was 10 mL/kg followed by a second dose of 5 mL/kg in which the K^+ content was reduced to 10 mEq/L 20 minutes after cross-clamping. Additional cardioplegia was given until complete diastolic arrest (absence of all electromechanical activity) was achieved.

ANTEGRADE CARDIOPLEGIA. In 10 animals, cardioplegia was given through a catheter inserted through the aortic root (9F, DLP). The aortic root pressure was not allowed to exceed 70 mm Hg during the infusion period. After the infusion of cardioplegia, the same catheter was used to vent the left ventricle by gravity drainage.

RETROGRADE CARDIOPLEGIA. In 10 animals, cardioplegia was given through a catheter inserted into the coronary sinus (9F, DLP) through a pursestring in the right atrium.

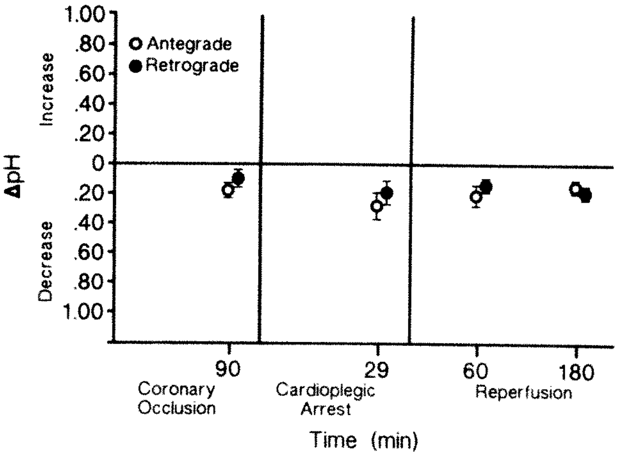

Fig 1. Changes in myocardial pH (ΔpH) in the circumflex artery distribution. There is minimal change in ΔpH in either the antegrade or retrograde hearts in the unobstructed circumflex artery territory.

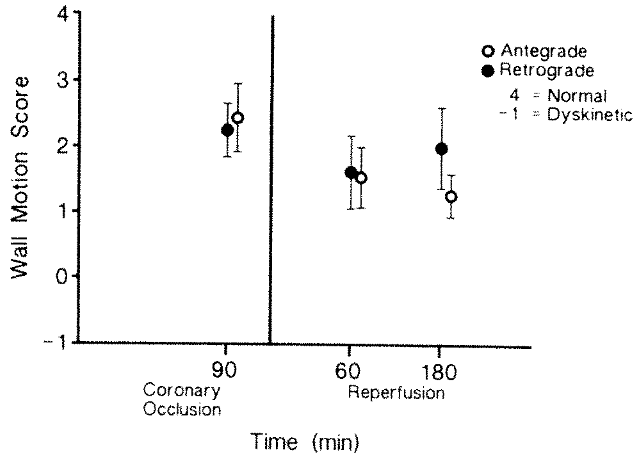

Fig 3. Wall motion scores. Both groups have lower wall motion scores after 90 minutes of coronary occlusion. After 180 minutes of reperfusion, wall motion scores tend to be higher in the retrograde group.

The catheter was positioned such that when the balloon was inflated, it was just beyond the orifice of the coronary sinus. Coronary sinus pressure was continuously monitored and not allowed to exceed 50 mm Hg. During cardioplegia infusions and throughout the arrest period, the left ventricle was vented with a 9F catheter in the ascending aorta by gravity drainage.

After the 30-minute arrest period, the aortic cross-clamp was removed, the coronary snares were released, and all hearts were reperfused for 3 hours on cardiopulmonary bypass at 37°C.

Results

The results are summarized in Figures 1 through 4.

Time to Arrest and Cardioplegic Volumes

Hearts treated with retrograde cardioplegia took longer to achieve full diastolic arrest (225 ± 46 versus 22 ± 4 seconds; $p < 0.0001$) and required larger amounts of cardioplegia for the initial dose (1,119 ± 153 versus 371 ± 13 mL; $p < 0.0001$).

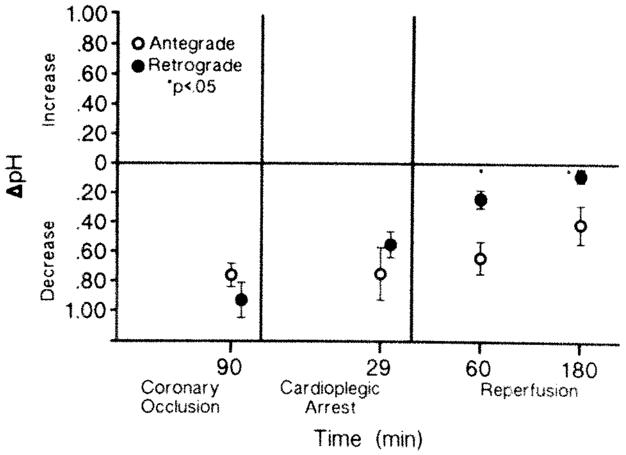

Fig 2. Changes in myocardial pH (ΔpH) in the diagonal distribution. Both groups have decreased pH after 90 minutes of coronary occlusion. During cardioplegic arrest, pH values tend to be higher in the retrograde group. During reperfusion, pH values are significantly higher in retrograde cardioplegia–protected hearts.

Temperature During Arrest

There was no difference in average myocardial temperature in the circumflex artery distribution between the two cardioplegic groups (13.7° ± 0.8°C retrograde versus 13.3° ± 0.8°C antegrade; not significant [NS]). Although myocardial temperature was slightly higher in the area at risk between the occluded diagonal vessels, there was no difference in average temperature between retrograde and antegrade cardioplegia hearts (14.8° ± 0.6°C versus 15.3° ± 1.2°C; NS).

Changes in Myocardial pH

The changes in myocardial pH are summarized in Figures 1 and 2. Before coronary artery occlusion, there was no difference in myocardial pH in the circumflex distribution between the retrograde and antegrade cardioplegic groups (7.39 ± 0.08 versus 7.36 ± 0.07; NS). There were minimal changes in pH in the circumflex distribution from preischemic levels in both the retrograde and antegrade

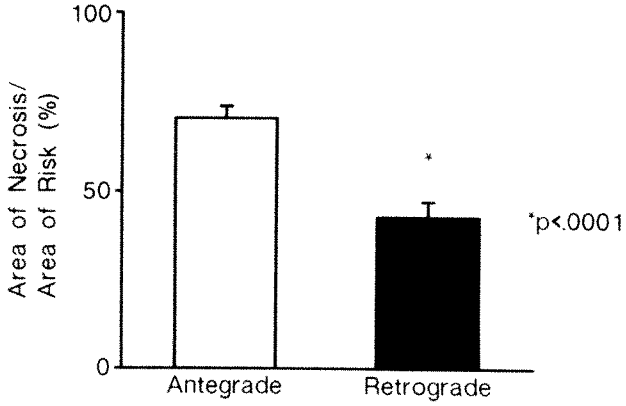

Fig 4. Area of necrosis/area of risk. Hearts protected with retrograde cardioplegia have significantly less myocardial necrosis.

cardioplegic hearts during the periods of coronary occlusion, cardioplegic arrest, and reperfusion (see Fig 1).

All hearts showed a significant decrease in pH from control levels in the myocardium distal to the coronary occlusions (see Fig 2). This trend persisted during the period of cardioplegic arrest. However, during the period of reperfusion, hearts treated with retrograde cardioplegia showed significantly less change in pH from preischemic levels at 1 hour (change in pH, 0.24 ± 0.06 retrograde versus 0.64 ± 0.11 antegrade; $p < 0.01$) and 3 hours (0.08 ± 0.03 retrograde versus 0.41 ± 0.13 antegrade; $p < 0.05$).

Wall Motion Scores

Coronary artery occlusion resulted in significant depression in wall motion in both groups after 90 minutes of ischemia (see Fig 3) (2.25 ± 0.41 retrograde [$p < 0.05$ versus preischemia] and 2.44 ± 0.52 antegrade [$p < 0.05$ versus preischemia]). Wall motion remained depressed in both groups during the reperfusion period; however, scores tended to be higher in hearts treated with retrograde cardioplegia (2.00 ± 0.62 versus 1.27 ± 0.33; NS).

Histochemical Staining

The area of risk of the ventricle beyond the coronary occlusions was similar in both groups (9.46% ± 0.75% retrograde versus 11.1% ± 0.91% antegrade; NS). However, hearts protected with retrograde cardioplegia had significantly less infarcted tissue in the area at risk (43.4% ± 3.6% versus 73.3% ± 3.5%; $p < 0.0001$) (see Fig 4).

Comment

There is currently a renewed interest in the coronary sinus as a vehicle for myocardial protection and as a route to stabilize actively ischemic myocardium and minimize the effects of reperfusion [10]. In recent years, retrograde coronary sinus cardioplegia has emerged as an alternative method for myocardial protection [11].

There are several potential advantages to using retrograde cardioplegia. During an aortic valve replacement, it avoids the risk of trauma to the coronary artery by direct ostial cannulation [12]. It obviates the need to interrupt a surgical procedure such as an aortic valve replacement [13]. During reoperative coronary artery bypass grafting, it may minimize the problem of distal embolization of atheromatous material that can collect in saphenous vein grafts. Most importantly, it has been shown to provide more uniform distribution of cardioplegia beyond coronary stenoses [2–4]. Shapira and associates [14], using myocardial thermograms, showed that in the presence of severe and extensive coronary artery disease, retrograde coronary sinus cardioplegia resulted in more homogenous cooling of the myocardium than was possible with antegrade cardioplegia. Gundry and Kirsh [2], in a canine model using left anterior descending coronary artery occlusion during a 2-hour cross-clamp period, showed a similar result. In addition, they observed that this superior distribution of cardioplegia during arrest resulted in more complete return of systolic and diastolic function during reperfusion in the area beyond the occlusions. In a similar model of left anterior descending coronary artery occlusion in the dog, Partington and co-workers [3] used microspheres to show that retrograde coronary sinus cardioplegia was superior to antegrade cardioplegia in delivering nutritive flow to areas supplied by occluded vessels. Whereas antegrade cardioplegic perfusion resulted in a redistribution of flow away from the subendocardial muscle in the presence of an occlusion, retrograde cardioplegia maintained preferential flow to the vulnerable subendocardial muscle. Despite these favorable experimental studies, clinical studies by Fiore, Bhayana, and their associates [5, 6] in patients undergoing coronary artery bypass grafting could show no additional benefits from retrograde cardioplegia over antegrade techniques. These studies, however, consisted of patients with normal ejection fractions and stable angina patterns. A more efficacious test of the possible advantages of retrograde cardioplegia would be in patients undergoing revascularization for acute coronary ischemia as occurs after a failed percutaneous transluminal coronary angioplasty.

Although no experimental study can ever completely mimic a clinical syndrome, we believe that our model of acute coronary occlusion in the pig with subsequent revascularization closely simulates the events that occur after a failed percutaneous transluminal coronary angioplasty leading to coronary artery bypass grafting. In our studies, the occlusion of the second and third diagonal vessels off the left anterior descending coronary artery has consistently resulted in an area of risk of approximately 10%. These animals remain off cardiopulmonary bypass for 90 minutes, thus simulating the ongoing coronary ischemia that occurs after a failed percutaneous transluminal coronary angioplasty. This model also allows us to define exactly the area of risk and to determine the effects of revascularization on pH, wall motion, and histochemical staining. These variables can be more precisely measured in our experimental model than in clinical studies. By using the right heart bypass technique to detect wall motion changes, afterload is kept consistent and echo sections can be compared during ischemia and reperfusion at matched end-diastolic volumes. Most importantly, histochemical staining techniques provide a more accurate measurement of ischemic necrosis [7, 8].

Our results clearly show that in the setting of emergent revascularization for an acute coronary occlusion, retrograde coronary sinus cardioplegia results in significantly less myocardial necrosis than with antegrade cardioplegia (see Fig 4). This occurs despite the absence of significant improvement in wall motion scores in the area of risk between the two cardioplegic techniques (see Fig 3). We suspect that this persistent depression in systolic shortening is due to "stunned myocardium" and provides further evidence that depressed wall motion immediately after reperfusion is not a valid index of myocardial necrosis [15]. During the period of cardioplegic arrest, there was no difference in temperature between the two cardioplegic techniques. However, there appeared to be less acidosis in the retrograde group in the area of risk immediately before aortic unclamping, although this did not reach statistical significance (see Fig 2). We suspect that the short cross-clamp time combined with the use of topical and systemic hypothermia may have masked the temperature differences seen in previous studies comparing retrograde and antegrade cardioplegia [2–4]. Nevertheless, there was significantly less tissue acidosis in the area at risk during reperfusion, suggesting that this area received more uniform cardioplegic distribution during arrest. As in previous studies, we observed no difference in the degree of protection provided by either technique in the areas of myocardium supplied by unobstructed vessels [3, 4].

Our results were also consistent with previous clinical and experimental studies showing that hearts protected with retrograde cardioplegia take longer to achieve a complete arrest and require larger amounts of cardioplegia for the initial dose [4, 6, 16]. Although it could be argued that the decrease in ischemic necrosis in the retrograde group was secondary to the larger volumes of cardioplegia administered, this was offset by the longer time needed for electromechanical arrest and the increased utilization of adenosine triphosphate. In addition, previous experimental studies have shown that larger volumes of cardioplegia administered by continuous antegrade techniques do not result in any better preservation of energy stores, myocardial ultrastructure, water content, or ventricular function than is possible with smaller volumes delivered with multidose cardioplegia [17, 18]. In a similar study in the porcine model with 2 hours of left anterior descending coronary artery occlusion during ischemic arrest, we have shown that larger amounts of antegrade continuous cardioplegia failed to lower temperature, decrease tissue acidosis, or improve regional function compared with smaller multidose volumes [19]. Hence, it is not the volume of cardioplegia delivered, but the ability of the cardioplegic solution to reach those areas of the myocardium beyond a critical coronary occlusion that determines the level of myocardial protection that is achieved. We agree with Partington and associates [4] that the combination of antegrade plus retrograde delivery of cardioplegia avoids the problem of having to deliver larger volumes of cardioplegia to achieve a fast arrest.

In this experimental model, antegrade cardioplegia was given only through the aortic root. It is conceivable that if antegrade cardioplegia was given through a completed vein graft immediately after the distal anastomosis to the area of risk, the degree of ischemic necrosis in the antegrade group may have equaled that of the retrograde group. Nevertheless, this study suggests that retrograde coronary sinus cardioplegia may significantly decrease the degree of myocardial necrosis after urgent surgical revascularization for acute coronary occlusions compared with standard antegrade techniques.

The secretarial assistance of Ellie LaBombard and Deborah Cammarata in the preparation of the manuscript is greatly appreciated.

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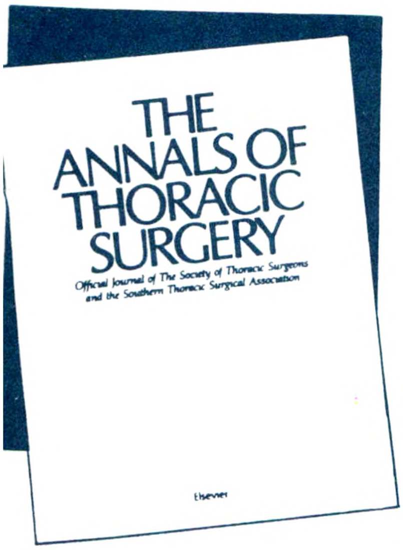
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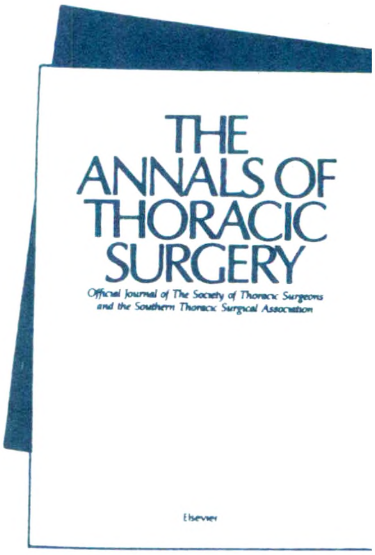
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End-to-End Repair of Aortic Coarctation Using Absorbable Polydioxanone Suture

Juan D. Arenas, MD, John L. Myers, MD, Marie M. Gleason, MD,
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Based on previous laboratory work, we have used polydioxanone absorbable suture in a variety of vascular and cardiac repairs in pediatric patients. However, some investigators have expressed concern about the potential for aneurysm formation at the anastomotic site. Between March 1983 and June 1989, 15 patients (7 male, 8 female) aged 2.5 months to 9.2 years (mean, 3.7 years) had resection of coarctation of the aorta and end-to-end anastomosis with polydioxanone absorbable suture. Thirteen patients have returned for routine postoperative evaluation, the follow-up time ranging from 11 to 49 months (mean, 23 months). Noninvasive two-dimensional, pulsed-wave Doppler and color echocardiography and magnetic resonance imaging studies demonstrated good anatomical repair and no anastomotic aneurysm formation or residual coarctation of the aorta in any patient after end-to-end anastomosis with polydioxanone. In summary, this intermediate follow-up study has revealed no vascular complications related to the repair of coarctation with absorbable polydioxanone suture.

(Ann Thorac Surg 1991;51:413–7)

One long-term complication after surgical repair of coarctation of the aorta (CoA) is residual or recurrent coarctation. Different suture materials have been employed in an attempt to avoid this problem [1, 2]. In general, we perform subclavian flap angioplasty in neonates and most infants with aortic coarctation who are less than 1 year of age [3]. Older children usually undergo resection of the coarctation and end-to-end anastomosis. Previously published work shows the advantages of polydioxanone (PDS), an absorbable monofilament suture, over polypropylene (Prolene), a nonabsorbable monofilament suture, in growing anastomoses [1, 2, 4]. These studies demonstrated that PDS allows the vascular anastomoses to grow.

Since 1983, we have used PDS suture in a variety of cardiovascular procedures [4]. However, some concerns have been expressed regarding aneurysm formation at the vascular anastomotic site when absorbable sutures are used [5]. This report describes the results in 15 consecutive patients who had resection of CoA and end-to-end anastomosis using PDS absorbable suture.

Patients and Methods

Study Population

Between March 1983 and June 1989, 15 patients aged 2.5 months to 9.2 years (mean, 3.7 years) had a surgical repair of CoA consisting of CoA resection and end-to-end anastomosis using PDS monofilament absorbable suture at The Milton S. Hershey Medical Center. Seven patients were male and 8 were female. Their weight at operation ranged from 5 to 26.9 kg (mean 15.4 kg).

Preoperative cardiac catheterization in 13 patients

Table 1. Preoperative Data

Patient No.	Sex	Weight (kg)	Age at Operation (y)	Catheterization Gradient (mm Hg)
1	F	16.6	6.1	20
2	F	14.0	2.3	. . .
3	F	14.3	3.0	70
4	F	18.5	4.6	50
5	F	5.5	0.7	35
6	M	15.0	3.8	35
7	M	8.7	1.0	45
8	M	30.0	7.3	50
9	M	10.5	1.4	50
10	M	5.0	0.2	. . .
11	M	19.5	5.2	. . .
12	F	13.0	1.8	30
13	M	25.0	7.8	30
14	F	15.7	4.2	40
15	F	26.9	9.2	50
Mean		15.1	4.9	42.7
SEM		2.1	0.8	3.6

SEM = standard error of the mean.

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showed CoA gradients that ranged from 30 to 70 mm Hg (mean, 43 mm Hg). Mean age at catheterization was 3.6 years. Associated cardiac anomalies were ventricular septal defect in 3 patients, patent ductus arteriosus in 1 patient, and bicuspid aortic valve in 6 patients. One patient had patent ductus arteriosus ligation before CoA repair (Table 1).

Operative Technique

Through a left fourth intercostal space thoracotomy, the entire aorta from the aortic arch to the diaphragm was mobilized. The patent ductus arteriosus or ligamentum arteriosum was ligated before excision of the CoA segment. An end-to-end anastomosis was performed with continuous PDS sutures on the posterior aspect of the aorta and interrupted PDS sutures on its anterior aspect. The aortic cross-clamp time ranged from 18 to 50 minutes (mean, 34 minutes).

Postoperative Management

A right radial artery catheter was used to monitor blood pressure continuously. Sodium nitroprusside and intravenous propranolol or esmolol were used to control systemic hypertension in the immediate postoperative period to maintain peak systolic blood pressure at between 100 and 110 mm Hg. If hypertension persisted, regimens of oral captopril or propranolol or both were begun on the day after operation. Urine output was measured, blood chemistry tests for renal function were done, and stool was tested postoperatively for occult blood.

Intermediate-Term Evaluation

Thirteen patients returned to the pediatric cardiology clinic for routine postoperative evaluation. Two patients did not show up for their follow-up appointments. They were both well, as could be determined by telephone assessment. Follow-up ranged from 11 to 49 months (mean, 23 months) postoperatively.

Electrocardiograms, chest radiographs, and routine physical examination including blood pressure measurements were obtained in all patients.

Complete two-dimensional, pulsed-wave Doppler and color flow mapping echocardiography was performed successfully in 12 of the 13 patients using a Vingmed CFM 500 (Interspec, Inc, Ambler, PA) ultrasound system. Imaging and Doppler echocardiography were performed with 5.0- and 3.0-MHz phased array transducers. One patient could not be adequately sedated for noninvasive testing. Chloral hydrate sedation (60 to 100 mg/kg orally) was administered to the patients less than 3 years of age who were unable to cooperate. The aortic arch and the site of repair were imaged from the suprasternal notch to evaluate for residual CoA or anastomotic aneurysm. Ascending and descending aortic velocities were measured with high pulse repetition frequency pulsed-wave and continuous-wave Doppler echocardiography.

Successful magnetic resonance imaging of the aortic arch was completed in 11 of the 13 patients, using a Siemens Magnetom 1.0-Telsa scanner (Siemens Medical Systems, Inc, Islan, NJ). Chloral hydrate sedation was administered to uncooperative patients less than 6 years of age. Parental permission was obtained for the magnetic resonance imaging scan. One patient could not be adequately sedated and 1 patient did not show up for his appointment at the magnetic resonance imaging facility.

Results

Clinical Status

On the first postoperative day, 6 patients had serious hypertension, which was treated with sodium nitroprusside and propranolol to lower the systolic arterial blood pressure to between 100 and 110 mm Hg. Subsequently, antihypertensive medication was required in 6 patients, 3 patients received captopril for 2 to 4 weeks, and 3 patients received β-blockers for 2 to 4 weeks. In all but 1 patient, antihypertensive medication was discontinued within 1 month postoperatively. This patient no longer required antihypertensive medication at 2 months postoperatively. Six months postoperatively, neither systolic nor diastolic hypertension was present in any patient. Postoperative urine output and renal function tests were normal in all patients. Finally, neither paraplegia nor symptoms of intestinal ischemia occurred in any patient.

At the most recent examination, all patients were clinically well, had no cardiovascular symptoms, and were no longer taking any medications. Cardiac murmurs were audible at follow-up examination in the 3 patients with restrictive ventricular septal defects, in 2 patients with mitral valve prolapse and mild regurgitation, and in 6 patients with bicuspid aortic valves. All patients had normal peripheral artery pulses. Chest radiographs showed normal cardiac dimensions except for mild cardiomegaly in 1 child with a moderate ventricular septal defect. Eight of 13 patients had normal echocardiographic results; chest radiographs showed biventricular hypertrophy in the patient with a ventricular septal defect who had cardiomegaly. Right ventricular hypertrophy voltage criteria were present in 2 patients without residual CoA or associated aortic stenosis. One patient with mitral valve prolapse and mild mitral insufficiency had borderline left ventricular hypertrophy. One patient with a bicuspid aortic valve and mild aortic stenosis showed left-axis deviation and complete right bundle-branch block postoperatively.

Noninvasive Evaluation

Two-dimensional echocardiography did not suggest anastomotic aneurysm formation in any patient, and no residual CoA was detected in any patient after end-to-end anastomosis with PDS. Three patients showed mild narrowing at the anastomotic site compared with the dimensions of the ascending and descending thoracic aorta. Bicuspid aortic valves were noted in 6 of the 12 patients studied. Mitral valve prolapse was detected in 2 patients and restrictive perimembranous ventricular septal defects in 3 patients.

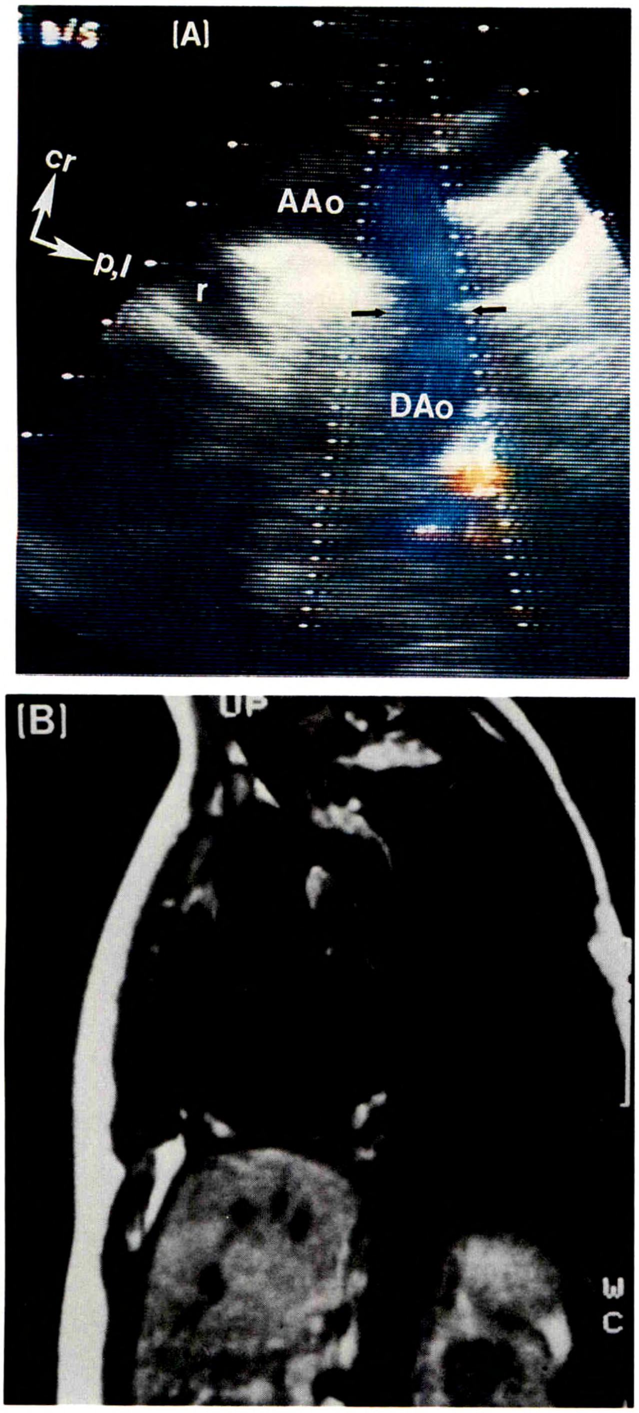

Fig 1. (A) Two-dimensional echocardiogram and color flow mapping of the aortic arch from the suprasternal notch (patient 1). Blue *indicates laminar blood flow away from the transducer.* Black arrows *indicate level of end-to-end anastomosis.* (AAo = *ascending aorta;* DAo = *descending aorta;* cr = *cranial;* l = *left;* p = *posterior;* r = *right pulmonary artery.) (B) Magnetic resonance image (sagittal view) of the aortic arch (patient 1).*

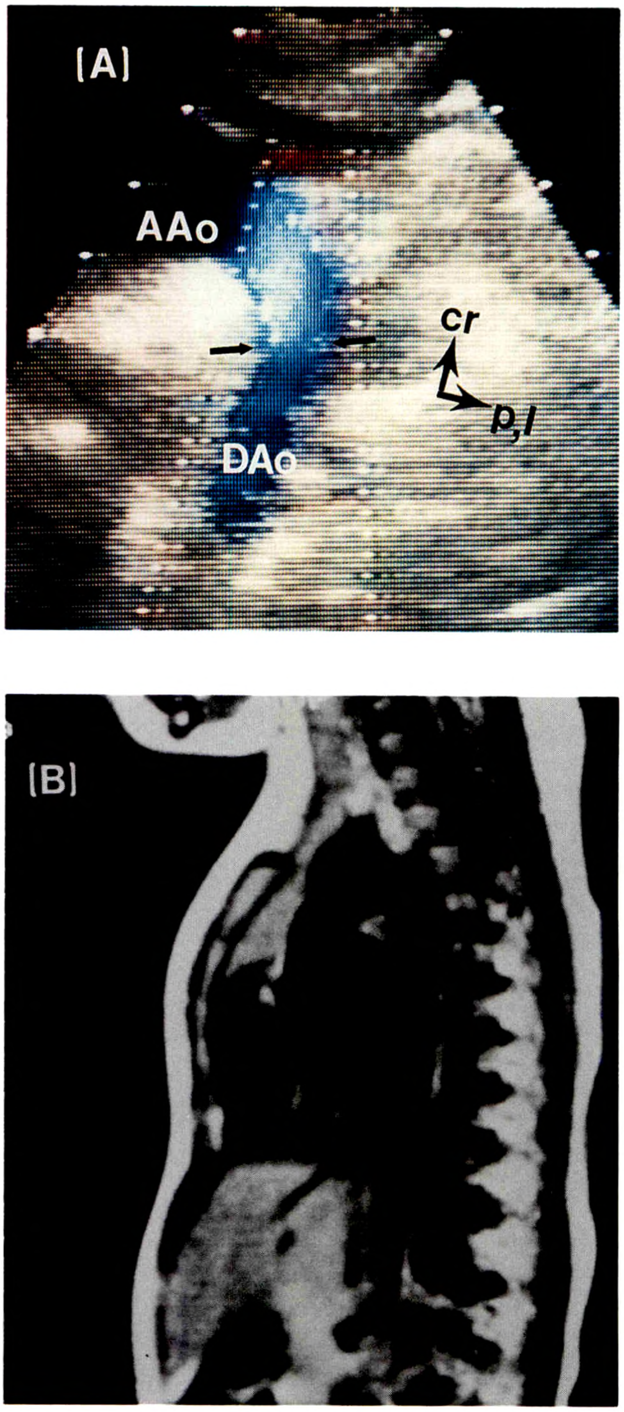

Fig 2. (A) Two-dimensional echocardiogram and color flow mapping of the aortic arch from the suprasternal notch (patient 5). Blue *indicates laminar blood flow away from the transducer.* Black arrows *indicate level of end-to-end anastomosis.* (AAo = *ascending aorta;* DAo = *descending aorta;* cr = *cranial;* l = *left;* p =*posterior;* r = *right pulmonary artery.) (B) Magnetic resonance image (sagittal view) of the aortic arch (patient 5).*

Doppler echocardiographic evaluation of the ascending and descending aortic velocities defined the degree of associated aortic valve stenosis or residual aortic arch gradient using the modified Bernoulli equation [6]. Peak instantaneous aortic valve gradients ranged from 0 to 27 mm Hg (mean, 12 mm Hg) and peak instantaneous aortic

Table 2. Follow-Up Data

Patient No.	Follow-up (mo)	Doppler Arch Gradient (mm Hg)	LVSF[a]	Other Defects	Other Doppler	Blood Pressure (mm Hg)
7	49	9	0.43	BAV	AS	120/54
1	40	0	0.42	BAV	AS	90/50
8	31	9	0.38	VSD, MVP	MR	90/50
3	27	16	0.50	BAV	. . .	104/60
4	27	0	0.58	BAV	. . .	90/50
5	26	10	0.50	. . .	. . .	110/. . .
15	22	17	0.43	. . .	. . .	114/70
14	14	5	0.46	VSD	. . .	104/64
10	13	13	0.47	BAV	. . .	100/. . .
16	12	0	. . .	. . .	. . .	106/60
11	12	. . .	0.46	BAV, VSD	. . .	95/60
13	11	10	. . .	. . .	. . .	102/. . .
12	11	17	0.39	MVP	MR	104/58
Mean	25	8.75	0.468			
SEM	3.12	2.34	0.021			

[a] Normal > 0.28.

AS = mild aortic stenosis; BAV = bicuspid aortic valve; LVSF = left ventricular shortening fraction; MR = mitral regurgitation; MVP = mitral valve prolapse; SEM = standard error of the mean; VSD = ventricular septal defect.

arch gradients were 10 mm Hg or less (mean, 5 mm Hg) in 9 patients. Numerous studies have documented that Doppler maximal instantaneous gradient determinations significantly overestimate the peak-to-peak catheter gradient, especially with mild to moderate gradients [7, 8]. Four patients had instantaneous aortic arch gradients greater than 10 mm Hg (range, 13 to 17 mm Hg). Thus, there was no serious residual CoA in this group of patients.

Color mapping allows better visualization of the thoracic descending aorta than two-dimensional imaging alone. Often, the descending aorta distal to the left subclavian artery may be difficult to image, making the evaluation of aneurysm or recurrent CoA less reliable. Color flow mapping of the aortic arch showed virtually normal laminar flow in the descending aorta (Figs 1A, 2A) with minimal turbulence. Thus, the anatomy of the repair and blood flow characteristics were essentially normal in all patients postoperatively.

Magnetic resonance imaging studies provided excellent visualization of the entire aortic arch in all patients, but was particularly specific in defining the borders of the descending aorta in the area of the anastomosis (Figs 1B, 2B). In this group of patients, no aneurysm or recurrent CoA was noted on magnetic resonance imaging, thereby confirming the data obtained with two-dimensional echocardiography and color flow mapping. With this imaging technique, mild dilatation of the descending aorta distal to the suture line was noted in 5 patients and was attributed to poststenotic dilatation from preoperative jet hemodynamics (Table 2).

Comment

The use of absorbable suture material for vascular anastomoses allows growth of the vessel, which is necessary for a successful long-term result after surgical repair to prevent recoarctation in infants and children. A potential limitation of end-to-end repair with nonabsorbable suture is that it may limit normal growth at the anastomotic site and lead to recoarctation.

The use of noninvasive magnetic resonance imaging and two-dimensional color Doppler echocardiography allows the evaluation of hemodynamics and anatomical repairs and provides a reliable method by which to gain the information necessary for the postoperative evaluation of these patients.

Our previous experiments in a growing porcine model demonstrated that the use of PDS for vascular anastomoses provides a good anatomical repair, normal growth at the anastomotic site, and normal integrity during burst testing [1, 2]. Nevertheless, questions have been raised regarding the risk of aneurysm formation at the anastomotic site when using absorbable PDS [5].

Our prior experiences with animal models and our current experiences with children using PDS to repair CoA indicate good anatomical repair, good integrity of the anastomotic site, and physiological laminar blood flow characteristics, as well as adequate arterial growth and absence of recoarctation for as long as 49 months postoperatively. These results indicate that PDS is an acceptable material for repair of CoA in infancy and childhood and should continue to be used for the repair of vascular anastomoses in other forms of congenital heart disease.

Although a longer follow-up period, including periodical noninvasive assessments, will be required to determine the long-term integrity of aortic anastomoses with absorbable suture, the use of PDS absorbable suture has been shown to be safe and reliable in our clinical and experimental experience.

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Notice From the American Board of Thoracic Surgery Regarding Trainees and Candidates for Certification Who Are Called to Military Service Related to the Persian Gulf Conflict

The Board appreciates the concern of those who have received emergency call to military service. They may be assured that the Board will exercise the same sympathetic consideration as was given to candidates, in recognition of their special contribution to their country, during the Korean and Viet Nam conflicts with regard to deadlines, applications, examinations, and interruption of training.

Harvey W. Bender, Jr, MD
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Efficacy of Coronary Sinus Cardioplegia in Patients With Complete Coronary Artery Occlusions

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Myocardial areas distal to complete coronary artery occlusions are poorly protected by antegrade cardioplegia. We assessed the effects of coronary sinus cardioplegia in 30 patients undergoing bypass operations and at high risk of cardioplegic maldistribution because of the following anatomical patterns of coronary artery disease: critical (≥50%) stenosis of the left main trunk with total occlusion of the right coronary artery (16 patients) or critical (≥70%) stenosis of the right coronary artery with total occlusion of the left anterior descending (11 patients) or circumflex artery (3 patients). After induction of arrest through the aorta, coronary sinus cardioplegia was given intermittently during the cross-clamp period at a flow rate of 100 mL/min. Intraoperatively, occluded arteries were consistently found to be filled with the retrogradely infused solution. One patient died early postoperatively of low cardiac output and a second patient died later during his hospital stay, presumably of an arrhythmia. At autopsy, none of them had pathological evidence of inadequate myocardial protection. One patient sustained a myocardial infarction and 3 others required inotropes for more than 24 hours postoperatively. Postoperative values for right and left stroke volume indices were not significantly different from prebypass levels. Overall, these results are consistent with the occurrence of limited intraoperative ischemic damage and, by inference, suggest the efficacy of the coronary sinus route in preserving myocardial areas supplied by completely occluded coronary arteries and, hence, in jeopardy of inadequate cardioplegia delivery.

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Complete occlusion of a coronary artery represents a challenge for adequate delivery of cold cardioplegia and hence for adequate preservation of the myocardial area subserved by the occluded vessel [1–3]. In the past years, retrograde administration of cardioplegic solution through the coronary sinus has emerged as an attractive alternative to the various strategies of antegrade cardioplegic delivery [1, 4] because the coronary venous system represents an extensive and unobstructed network that is expected to behave as a very effective conduit for delivering core cooling and cardioplegic additives throughout the thickness of the myocardium. Stimulated by our favorable experience with the use of coronary sinus cardioplegia in valve operations [5] as well as by the consistent experimental demonstration that retrograde coronary sinus cardioplegia affords better protection to myocardial areas distal to coronary artery occlusions than do antegrade methods [6, 7], we undertook this observational study to assess the effects of the coronary sinus approach in a subset of patients undergoing coronary artery bypass grafting (CABG) and selected on the basis of a highly predictable risk of cardioplegic maldistribution because of multivessel disease involving at least the *complete* occlusion of a major coronary artery.

Material and Methods

Patient Population

Thirty consecutive patients undergoing isolated CABG were entered into this prospective study, which was approved by the Institutional Review Board. There were 24 men and 6 women who ranged in age from 45 to 79 years (mean, 69 years). Almost one half of the study group (12 patients) was 70 years of age and older. Eighteen patients had unstable angina [8], among whom 4 were receiving intravenous nitroglycerin therapy at the time of operation. Nineteen patients (63%) had experienced remote myocardial infarctions.

All preoperative coronary angiograms were reviewed by a single cardiologist (O.L.D.). Stenosis of the coronary arteries was estimated visually as the percentage of luminal cross-sectional area lost and usually was based on a composite of two projections. A serious lesion was defined as stenosis of 50% or more of the left main trunk and 70% or more for all other major coronary arteries. Based on these criteria, the patients could be classified into two groups. The first group consisted of 16 patients who had a serious stenosis of the left main trunk (9 patients) or its equivalent (7 patients) associated with a total occlusion of the right coronary artery. This occlusion involved the proximal segment of the right coronary artery in all patients but 1, in whom only the distal branches of the vessel were completely obstructed. Five of the 9 patients with left main stenosis had associated serious disease of both the left anterior descending and the circumflex

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coronary arteries. A second group consisted of 14 patients who had a serious stenosis of the right coronary artery (proximal to the bifurcation in 12 patients and distal to the bifurcation in 2 patients) associated with a total occlusion of one major left-sided coronary artery. This occluded artery was the left anterior descending in 11 patients and the circumflex artery in the 3 remaining patients. All left anterior descending occlusions originated proximal to the first diagonal branch and, in 9 of the 11 patients, were associated with a serious stenosis of the circumflex artery involving the proximal segment of the vessel (before the first obtuse marginal) in 8 patients and its distal segment in the remaining patients. In the 3 patients who had circumflex occlusion, the arterial lesions were proximally located and, in all patients, were associated with a serious stenosis of the left anterior descending. Overall, triple-vessel disease was present in 24 of our 30 patients (80%). For the whole group, the ejection fraction, calculated from a ventriculogram in the 30-degree right anterior oblique view, averaged 0.46 ± 0.13 (mean ± standard deviation).

Operative Technique

Cardiopulmonary bypass was established between the ascending aorta and the two individually cannulated venae cavae, which were snared shortly after the onset of bypass. The left ventricle was consistently vented through the right superior pulmonary vein. After application of the aortic cross-clamp, 1 L of crystalloid cardioplegic solution at 4°C was given through the aortic root. Supplemental doses (500 mL) of cardioplegia were subsequently delivered retrogradely into the coronary sinus approximately every 25 minutes during the period of global ischemia, yielding an average of two retrograde cardioplegic infusions per patient.

The technique of coronary sinus cardioplegia has already been extensively described [5]. Briefly, a short (2- to 3-cm) atriotomy is made on the anterior free aspect of the right atrium, parallel to the atrioventricular sulcus. The coronary sinus is cannulated with a specific retroperfusion catheter that features a manually inflatable pear-shaped balloon. Care is taken to keep the upper part of the inflated balloon seated around the intraatrial rim of the coronary ostium. The flow rate of the cardioplegia delivery system is fixed at approximately 100 mL/min, which prevents distal perfusion pressure from exceeding the safety limit of 40 mm Hg. The catheter is kept secured in the coronary sinus by means of balloon inflation throughout the arrest period. Ridges on the surface of the balloon further enhance self-maintenance of the device in the proper position. In addition to multidose cardioplegia, myocardial protection is provided by systemic cooling (25°C) and by topical hypothermia using ice slush.

All proximal and distal anastomoses were constructed during a single period of aortic occlusion. On average, every patient received three bypass grafts; 4 had an additional extensive endarterectomy of the left anterior descending artery, which was patched with graft implantation. The left internal mammary artery was used in 22 patients (73%). After the last anastomosis was completed, 1 L of a modified crystalloid reperfusate at 28°C was infused into the aortic root immediately before aortic unclamping [9]. The 5-minute period required for this last infusion was used for closing the right atriotomy with a continuous 5-0 polypropylene suture after catheter withdrawal. Because of the cardioplegic nature of the reperfusion solution, no attempts to defibrillate the heart were made until approximately 5 minutes had elapsed after removal of the aortic cross-clamp (during this time period, the heart is either asystolic or weakly fibrillating). The composition of the cardioplegic and reperfusion solutions is detailed in Table 1. The mean aortic cross-clamp time was 93 minutes (range, 66 to 135 minutes).

Table 1. Composition of Cardioplegic Solution and Reperfusion Solution

Variable	Cardioplegic Solution	Reperfusion Solution
K^+ (mEq/L)	12	15
Na^+ (mEq/L)	100	100
Mg^{2+} (mEq/L)	26	. . .
Ca^{2+} (mEq/L)	0.5	2.5
Cl^- (mEq/L)	100	100
Mannitol (g/L)	20	24.70
Glutamic acid (g/L)	2,942	2,942
pH	7.40 (at 20°C)	7.70 (at 28°C)
Osmolarity (mosm/L)	370	370

Assessment of Results

The postoperative records of the patients were reviewed for assessment of the following clinical endpoints. Operative mortality was defined as deaths occurring during the postoperative hospital stay or within 30 days of the operation. A perioperative myocardial infarction was diagnosed by the appearance of new Q waves on the electrocardiogram and postoperative low cardiac output was defined as more than $5\ \mu g \cdot kg^{-1} \cdot min^{-1}$ of inotropic support or intraaortic balloon support for more than 24 hours or more after bypass. Also recorded were the incidence of atrial and ventricular arrhythmias requiring medication, the time to extubation, and the cause of prolonged ventilatory support (>24 hours after bypass).

In addition, hemodynamic measurements were obtained before initiation of cardiopulmonary bypass and subsequently at 1, 6, 12, and 24 hours postoperatively using a radial arterial line and a pulmonary artery balloon-tipped catheter (VIP 93A-831H, Baxter Healthcare Corporation, Santa Ana, CA). Measurements recorded included systemic, right atrial, pulmonary artery, and pulmonary capillary wedge pressures and cardiac output (thermodilution technique). Using standard formulas [9], values for cardiac index and right ventricular and left ventricular stroke work indices were calculated at identical intervals. Comparisons between postoperative and prebypass values were made using the nonparametric Wilcoxon and Kruskal-Wallis tests. A p value of less than 0.05 was considered significant.

Table 2. Postoperative Recovery Profile for Right and Left Ventricular Stroke Volume Indices[a]

Variable	Before Bypass	After Bypass (h) 1	6	12	24
$\overline{\text{RAP}}$ (mm Hg)	9 ± 3	7 ± 3	9 ± 3	9 ± 2	10 ± 3
PCWP (mm Hg)	11 ± 4	11 ± 4	11 ± 5	12 ± 4	12 ± 3
$\overline{\text{PAP}}$ (mm Hg)	18 ± 4	18 ± 5	20 ± 5	19 ± 4	21 ± 5[b]
$\overline{\text{AoP}}$ (mm Hg)	85 ± 16	83 ± 15	74 ± 9[b]	75 ± 9[c]	84 ± 12
RVSWI ($g \cdot m/m^2$)	4 ± 3	4 ± 2	5 ± 4	5 ± 2	6 ± 3[b]
LVSWI ($g \cdot m/m^2$)	33 ± 16	26 ± 8	27 ± 6	30 ± 8	39 ± 14

[a] Results are expressed as mean ± standard deviation. [b] $p < 0.01$ versus the corresponding prebypass value. [c] $p < 0.02$ versus the corresponding prebypass value.

$\overline{\text{AoP}}$ = mean aortic pressure; LVSWI = left ventricular stroke work index; $\overline{\text{PAP}}$ = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; $\overline{\text{RAP}}$ = mean right atrial pressure; RVSWI = right ventricular stroke work index.

Results

There were two postoperative deaths. One patient died early in the intensive care unit of a low output syndrome that did not respond to inotropic drugs and intraaortic balloon pumping; multiple organ failure of rapid onset precluded an attempt at emergency heart transplantation. The second patient died suddenly the day before discharge, 1 week after operation. In spite of a massively dilated cardiomyopathy, which accounted for a low preoperative ejection fraction (0.25), he had had an uneventful postoperative course and presumably died of an arrhythmia. Interestingly, in neither of these 2 patients did the postmortem examination of the heart reveal left ventricular subendocardial hemorrhagic necrosis suggestive of inadequate intraoperative myocardial protection.

One patient sustained a nonlethal perioperative myocardial infarction and 3 patients (in addition to the 1 who died of a low cardiac output syndrome) required inotropic drugs for more than 24 hours postoperatively (1 of these patients was weaned from inotropic support by postoperative day 2 and the 2 others, by postoperative day 3). Except for the patient who died of low cardiac output, no patient required intraaortic balloon pumping postoperatively. Atrial and ventricular arrhythmias requiring drug therapy occurred in 10 and 3 patients, respectively. Twenty-seven of the 30 patients were extubated within 24 hours of operation. One had to be reintubated because of hemodynamic deterioration that ultimately led to death (see previous paragraph). This was the only patient in whom the cause of prolonged intubation was cardiac-related, as in the 3 patients who could not be extubated by postoperative day 1, the cause for prolonged ventilatory support was consistently pulmonary-related.

The postoperative hemodynamic profile of our patient population is depicted in Table 2. At none of the study points were the postoperative values of right and left ventricular stroke work indices significantly depressed, as compared with preoperative baseline levels. This finding deserves some consideration in view of the concomitant observation that with very few exceptions (see Table 2), the postoperative loading conditions of the two ventricles were virtually unchanged from the preoperative ones.

No complications related to coronary sinus cannulation or to retroperfusion were observed in the course of the study.

Comment

Rationale for the Use of Coronary Sinus Cardioplegia in the Presence of Coronary Artery Occlusive Disease

It has been demonstrated for several years that coronary artery occlusions limit the delivery of cardioplegic solution to the myocardial area distal to those occlusions [1, 2]. The resulting maldistribution of cooling and cardioplegia is now a well-identified cause of inadequate myocardial preservation [2, 3]. To overcome this problem, several strategies of antegrade cardioplegia delivery have been developed [1, 4] but their common limitation is to ensure delivery of cardioplegic flow beyond occlusions (or stenoses) only after the distal anastomoses have been completed. Further, none of these techniques avoids delayed protection of jeopardized myocardium that only becomes revascularized at the end of the cross-clamp period by means of an internal mammary graft, nor are they effective in preserving still-functional areas supplied by diseased but ungraftable vessels [4]. Additional topical cooling is undoubtedly helpful for reducing regional thermic gradients but its effectiveness is limited whenever the heart has to be lifted for completion of a right or circumflex distal anastomosis.

In this context, retrograde administration of cardioplegic solution through the coronary sinus has emerged as an appealing alternative because the coronary venous system represents an extensive and atherosclerosis-free network and appears therefore well suited for the delivery of core cooling and cardioplegic agents throughout the myocardium. This assumption is primarily based on anatomical studies that have shown that a retrogradely perfused solution can distribute at the capillary level in a left ventricular area supplied by a totally occluded coronary artery [10, 11]. It is therefore not unexpected that several experimental studies [6, 7] have demonstrated that in the presence of a coronary artery obstruction, retrograde cardioplegia afforded more homogeneous distribution of cardioplegic solution and better myocardial cooling distal to the obstruction as compared with antegrade methods, including high-pressure, high-viscosity blood cardioplegia, and that these patterns of improved distribution correlated with an improved recovery of postischemic function.

In contrast, the few clinical studies [12–15] that have addressed this issue have failed to demonstrate an unequivocal superiority of coronary sinus cardioplegia over the traditional techniques of antegrade cardioplegic administration. One possible explanation for these discrepant results lies in the acknowledgment by the authors of these clinical trials that their study patients were rather low-risk operative candidates, in particular with regard to the anatomical patterns of coronary artery disease. This consideration is important because thermovision studies performed during CABG in humans have shown that coronary artery stenoses up to 90% did not necessarily preclude adequate cooling of jeopardized myocardium by antegradely infused cardioplegia [16]. It is therefore conceivable that the coronary artery lesions of the patients enrolled in the aforementioned studies were not the most appropriate for the potential benefits of coronary sinus cardioplegia to be readily apparent. This assumption is supported by the observation that all the experimental studies that have documented the benefits of retrograde cardioplegia have dealt with animal models of *complete* coronary artery *occlusion* (as opposed to stenosis). Consequently, this specific anatomical pattern of coronary artery disease was selected as the basic inclusion criterion for the present study.

Methodological Issues

It is readily apparent that the major limitation of this study is that it does not include a control group in whom cardioplegia would have been given exclusively in an antegrade manner. The reason for this intentional flaw is the following: Our practice is to open the coronary artery to be grafted at the end of each cardioplegic infusion. In the past, we had noted that in patients with proximal total occlusion of the coronary arteries, there was no (or only minimal) cardioplegic fluid coming out of the arteriotomy when cardioplegia was given through the aortic root, thereby suggesting that reliance upon collateral circulation to deliver cardioplegic flow beyond occlusions was extremely hazardous. As we were gaining more experience with coronary sinus cardioplegia in valve operations [5], we started to expand its use to those coronary bypass patients who had total occlusion of a major coronary vessel. That such an approach was likely to be beneficial was then marshalled from the observation that the opened coronary artery was consistently found to be filled with retrogradely infused solution, thereby suggesting that the myocardial muscle distal to the occlusion was effectively reached by the cardioplegic retroperfusate. Comparison of myocardial temperatures between antegrade and retrograde cardioplegia was found to be more difficult to interpret because of the possibility for eventual between-group differences to be biased by our vigorous use of topical cooling. This issue, however, has been addressed by Shapira and associates [16]: Using temperature mapping by thermographic analysis during clinical CABG, these authors have demonstrated more uniform cooling in inflow-restricted regions with retrograde cardioplegia compared with aortic root cardioplegia (it is noteworthy that in this study, thermograms were taken before the application of topical hypothermia so that they truly reflect the myocardial cooling effects specifically exerted by each route of cardioplegia delivery).

Therefore, when we selected totally occlusive disease as a prerequisite for patients to be included in the present study, the prediction that this anatomical pattern would prohibit adequate delivery of cardioplegia by the antegrade methods led us not to study such a control group. A similar line of reasoning has actually been followed by Shapira and associates [17] in their study of coronary sinus cardioplegia in a patient population close to ours with respect to the pathological features of coronary arterial lesions. We do not think, however, that the observational nature of the present study brings into question some of the conclusions that can be drawn from its results.

Analysis of Results

A first observation relates to the safety of the technique. No complications related to retrograde coronary sinus perfusion were observed, an observation that is shared by the other authors who have used this approach during CABG [12, 14, 15]. The main technical guidelines that guarantee the safety of coronary sinus cardioplegia have been previously detailed [5] and, in brief, include positioning of the balloon at the ostium of the coronary sinus, avoidance of balloon overinflation, and maintenance of perfusion pressure below 40 mm Hg.

As far as efficacy is concerned, both the clinical course and the hemodynamic recovery patterns of our patients are consistent with an overall adequate myocardial preservation during ischemic arrest. Our raw data with regard to mortality, myocardial infarction, and postoperative cardiac failure compare favorably with those reported in the literature if one keeps in mind that coronary artery occlusion, per se, is itself a predictor of increased early mortality [18], and that many of our patients cumulated additional risk factors such as advanced age, unstable angina, and impaired left ventricular function [19]. One can argue that stroke work indices that were derived from our hemodynamic measurements may not accurately reflect the intrinsic state of ventricular contractility because of their load-dependence. However, in this study, loading conditions were kept within a fairly narrow range throughout the perioperative period (see Table 2), which gives some credit to our use of these indices for comparing ventricular function preoperatively and postoperatively. We acknowledge that this assessment is limited to global ventricular performance and, as such, does not allow us to make conclusions regarding preservation of regional myocardium beyond coronary artery occlusions. Nevertheless, it is intuitively appealing to assume that the consistent occurrence of a cardioplegic flow into the distal runoff of these occluded arteries had beneficial effects on the preservation of the corresponding myocardial areas.

However, it is evident that, by virtue of its design, this observational study does not allow us to conclude that the protection afforded by combined antegrade and retrograde cardioplegia is superior to what would have been obtained with the use of antegrade cardioplegia alone. Nor is our intention to persuade those content with antegrade techniques of cardioplegia delivery in patients with total coronary artery occlusions that they should switch to a combined approach. Rather, for those who are not fully satisfied with these antegrade techniques and therefore look for alternative strategies, we have attempted to document the results currently achievable when aortic root arrest is combined with intermittent retrograde delivery of cardioplegic solution through the coronary sinus.

Coronary Sinus Cardioplegia in Clinical Practice: Persisting Problems and Potential Solutions

Like any technique, the use of coronary sinus cardioplegia raises some concerns, most of which can be easily addressed. Delay in the onset of arrest can be avoided by delivering the initial dose of cardioplegia through the aortic root [20], although the true usefulness of this antegrade cardioplegic induction can be questioned in view of the excellent clinical results reported by some groups with the exclusive use of the coronary sinus route in both valve [5] and CABG [12, 14, 17] procedures.

Inadequate protection of the right ventricle does not seem to be a clinically relevant concern provided that the inflated balloon is kept at the ostium of the sinus and therefore does not impede delivery of cardioplegic flow into the terminal branches of the sinus [5]. Using radionuclide techniques, we [21] have previously shown that coronary sinus cardioplegia did not impair right ventricular function after aortic valve replacement. In the setting of bypass operations, this observation has been confirmed by Guiraudon [12], Fiore [14], and their co-workers and is further supported by the present findings that the postoperative values of right ventricular stroke work index yielded by our patients were virtually unchanged from prebypass values at fairly comparable levels of preload (reflected by mean right atrial pressures) and afterload (reflected by mean pulmonary artery pressures; see Table 2). It is likely that the discrepancy between the efficacy of coronary sinus cardioplegia in preserving right ventricular function clinically and the experimental observations made in dogs that the right ventricle receives relatively little cardioplegic solution from the coronary sinus route [10, 11, 22] is largely due to species differences in the right ventricular venous drainage patterns [10, 21]. In clinical practice, protection of the inside of the right ventricular cavity is also expected to result from the cooling effect exerted by that fraction of the retroperfusate which shunts the capillary bed and directly escapes into the right heart chambers [10]. It also sounds reasonable to speculate that the routine use of topical cooling further contributes to right ventricular preservation [14, 17].

Cannulation of the coronary sinus under direct vision, with its attendant necessity for bicaval cannulation and snares, can be of concern for those who routinely use single venous cannulation. This problem can now be solved by the use of stylet-guided catheters, which are advanced blindly into the coronary sinus through a stab wound in the right atrial wall.

In conclusion, the results obtained in a patient population at high risk of cardioplegic maldistribution suggest the occurrence of limited intraoperative ischemic damage and, by inference, the ability of a strategy of combined cardioplegia delivery (ie, induction of arrest through the aorta and subsequent maintenance of cardioplegia through the coronary sinus) to adequately preserve myocardial areas distal to *complete* chronic coronary artery occlusions. Additional studies are warranted to better define the indication for use of this combined approach in the other subsets of patients who are also at high risk of inhomogeneous cardioplegic delivery, such as patients with acute coronary artery occlusion after failed balloon angioplasty or patients undergoing redo bypass operations [23].

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Replacement of the Aortic Valve or Root With a Pulmonary Autograft in Children

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Between January 1967 and December 1988, 34 patients ranging in age from 3 to 18 years (mean, 14 ± 3.6 years) underwent replacement of the aortic valve or root with their own pulmonary valve. The indication for operation was left ventricular outflow obstruction in 16 patients (47%), aortic regurgitation in 14 (41%), mixed aortic valve disease in 3 (9%), and failure of a previously implanted aortic homograft in 1 (3%). There were four early deaths, all before 1971, giving a hospital mortality of 11.8% (70% confidence interval, 6% to 20%). Surviving patients have been followed up a cumulative total of 214 patient-years, the longest period of observation being 16 years 8 months. Late mortality was 13.3% (70% confidence interval, 7% to 23%), and 4 other patients required removal of the pulmonary autograft for endocarditis. Actuarial rates at 16 years were 74% ± 11% for freedom from reoperation on the left ventricular outflow tract, 80% ± 10% for freedom from reoperation on the right ventricular outflow tract, and 77% ± 10% for late survival. There was no instance of primary structural degeneration in the pulmonary autograft, and all surviving patients were in New York Heart Association functional class I without medication. This experience demonstrates that the pulmonary autograft can achieve good early and medium-term results in young patients. Should growth potential be realized, it might constitute the ideal biological valve for the left ventricular outflow in children.

(Ann Thorac Surg 1991;51:424–9)

After the discovery of accelerated structural degeneration in young patients [1–3], porcine and pericardial valves were largely abandoned in favor of mechanical prostheses for children. Yet, it is the young patient, with a potential life span of 50 to 60 years, who is ultimately most vulnerable to the cumulative effects of valve-related complications and whose myocardium will accrue the consequences of any hemodynamic imperfection in an aortic valve substitute. The pulmonary autograft, like an aortic homograft, offers advantages of central laminar flow and freedom from prosthetic sounds, hemolysis, and anticoagulation. In addition, it is living autogenous tissue which, theoretically, could function indefinitely and grow with the patient. In this report we review our experience with the pulmonary autograft for aortic valve or aortic root replacement in children.

Patients and Methods

Patients

Between January 1968 and December 1988, 34 patients 18 years of age or younger underwent aortic valve or aortic root replacement with their own pulmonary valve. There were 27 male and 7 female patients. Age at operation ranged from 3 to 18 years (mean ± standard deviation, 14 ± 3.6 years). Previous surgical procedures on the left ventricular outflow tract included open aortic valvotomy in 8 patients, homograft replacement of the aortic valve in 1 , enucleation of subaortic stenosis in 2, and conservative repair of aortic regurgitation in 1. In addition, 2 patients had undergone prior repair of aortic coarctation. The underlying pathology was identified as a congenital bicuspid valve in 8 patients (23%), rheumatic valve disease in 8 (23%), and bacterial endocarditis in 5 (15%). At the time of operation, 22 patients (65%) were in New York Heart Association functional class I and 12 (35%), in class II.

Preoperative evaluation included cardiac catheterization and angiography in all patients. This demonstrated the anatomy of the left ventricular outflow tract and coronary arteries, as well as the degree of obstruction or regurgitation at the aortic valve. Mean gradient across the aortic valve was 71 ± 38.4 mm Hg. More recently, real time and Doppler echocardiography have been used also to evaluate left ventricular size, aortic root diameter, and the type of aortic dysfunction.

Surgical Techniques

All operations were performed on cardiopulmonary bypass with moderate hypothermia, using a single right atrial basket for venous drainage and arterial return to the ascending aorta. Details of the technique have evolved over the years [4–6]. At present, the aortic valve is first inspected, and coronary perfusion is established, both for myocardial preservation and to facilitate the identification of major coronary artery branches during subsequent removal of the pulmonary valve. It is important to confirm that the pulmonary valve is normal, and this is done early through a transverse incision in the main pulmonary artery just above the valve sinuses. The pulmonary valve

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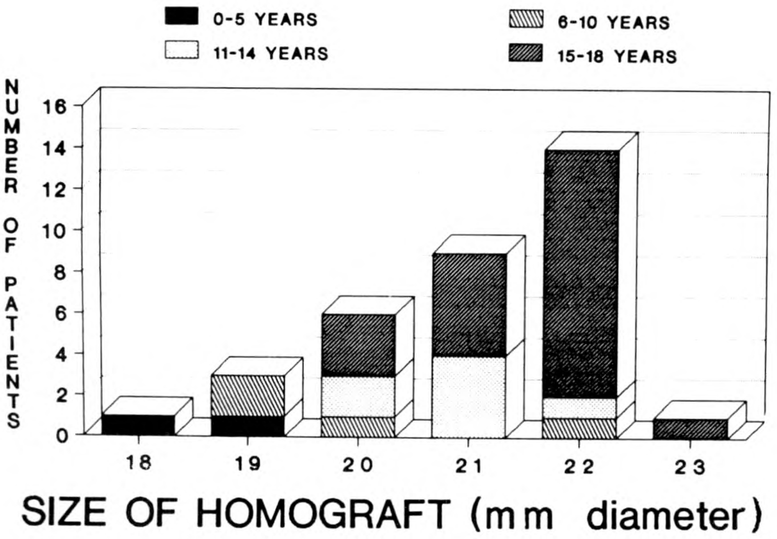

Fig 1. Size of pulmonary or aortic homograft used for reconstruction of the right ventricular outflow tract at various ages.

is then removed with a supporting cuff of right ventricular myocardium, taking care to preserve the first septal branch of the anterior descending coronary artery [7].

Blood or crystalloid cardioplegia is used to relax the myocardium for reconstruction of the right ventricular outflow tract; cardioplegic arrest, supplemented with topical cooling, is continued until aortic valve replacement has been completed or until the left coronary artery has been implanted into the new aortic root. The right ventricular outflow tract was reconstituted with either an aortic homograft (fresh, 20; cryopreserved, 2; freeze-dried, 3) or a pulmonary homograft (fresh, 7; cryopreserved, 9). Our present preference is a fresh or cryopreserved pulmonary homograft. The size of homograft used for right ventricular outflow reconstruction at various ages is summarized in Figure 1.

When the pulmonary autograft was used for aortic valve replacement (31 patients), implantation was done with a lower suture line of multiple interrupted simple stitches and a continuous upper suture line. The sinuses of the autograft were scalloped to accommodate the coronary orifices [5]. Insertion of the pulmonary autograft for complete aortic root replacement (3 patients) was carried out essentially as described previously for aortic homograft root replacement [8]. The right coronary was reimplanted after the distal aortic anastomosis was completed and the aortic cross-clamp was released, to determine the correct site in the distended autograft.

The duration of cardiopulmonary bypass ranged from 111 to 184 minutes, with an average of 133 minutes. Associated procedures were carried out in 4 patients (12%), including a septal myectomy in 4 patients and enucleation of a discreted subaortic stenosis in 1 patient [9].

Homograft Valve Procurement

Aortic and pulmonary valves with as much length as possible of their respective distal vessel were collected from postmortem donors within 48 hours of death, sterilized in antibiotic solution, and stored in a tissue culture medium at 4°C [10]. Alternatively, in the preparation of cryopreserved valves, 15% glycerol was added to the nutrient antibiotic solution for 24 hours before freezing. The frozen valves were stored in liquid nitrogen vapor. ABO cross-matching was not performed routinely in this series.

Follow-up

All patients were reviewed at least annually with clinical examination and chest radiograph, the closing interval being December 1988. More recently, echocardiograms and Doppler studies have been carried out also. At least one echocardiographic study was available in 18 of the 22 autografts (81.8%) functioning at the time of review, and serial studies were available in 6 patients (Table 1). A typical echocardiographic study is illustrated in Figure 2. The patient's status was determined by retrospective review of all clinical notes and, when available, postmortem or laboratory reports. The longest follow-up was 16 years 8 months, and cumulative total follow-up was 214 patient-years. Twelve patients were observed for longer than 14 years. Valve-related complications were categorized according to the criteria of Edmunds and associates [11].

Statistical Analysis

Standard actuarial methods were used to analyze valve-related complications and patient survival [12]. Where applicable, continuous variables have been presented as the mean ± one standard deviation. Alternatively, 70% confidence intervals of the mean have been given for proportions.

Results

Early Mortality

There were four early deaths giving a hospital mortality of 11.8% (70% confidence interval, 6% to 20%). Two patients died of low cardiac output secondary to myocardial infarction, which resulted from damage to the first septal

Table 1. Serial Echocardiographic Measurements of Pulmonary Autograft Diameter in the Left Ventricular Outflow Tract

Age at Operation (y)	Follow-up Time (mo)	Autograft Diameter (mm)
3	1	11
	39	19
12	1	19
	26	21
	59	24
15	1	19
	19	21
	51	23
16	1	18
	45	22
16	1	21
	4	22
	33	23
17	1	23
	25	23
	68	23
	92	24

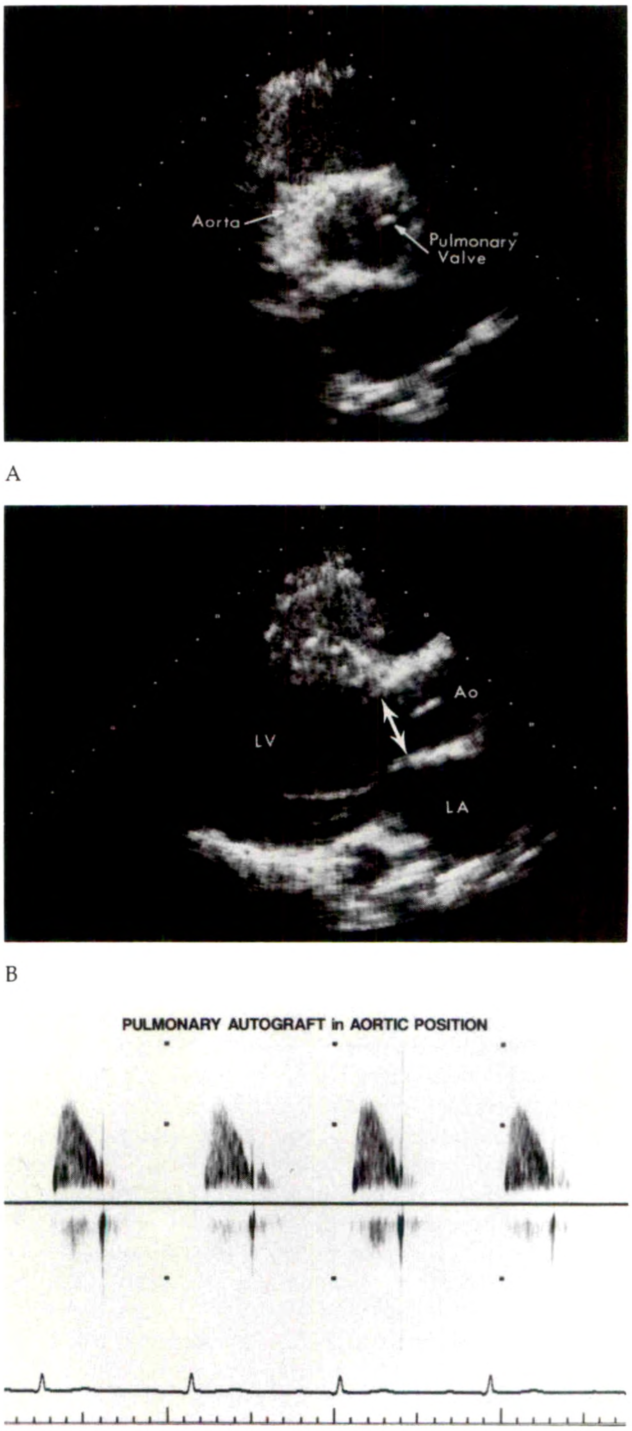

Fig 2. Real-time echocardiogram of a pulmonary autograft in the short-axis (A) and long-axis (B) views. The site of measurement for the diameter of the autograft is shown at the ventriculoarterial junction, as well as normal leaflet motion. Doppler flow across the valve (C) confirms the absence of serious stenosis or regurgitation, in this case, 18 months after implantation. (Ao = *aorta;* LA = *left atrium;* LV = *left ventricle.)*

branch of the left anterior descending coronary artery [7]. One patient died of a sudden arrhythmia, which also may have resulted from ischemic injury to the conduction tissue. The final death was due to complications of renal failure. There have been no hospital deaths since 1971.

Late Mortality

Four patients died during the period of follow-up (13.3%; 70% confidence interval, 7% to 23%). One patient died suddenly 2 months after operation, probably as the result of an arrhythmia. Postmortem examination showed no abnormality in either ventriculoarterial valve. One patient died after 8 years of a pulmonary embolus, and another, at 14 years with miliary tuberculosis. The cause of death was not established in the fourth patient, who died 4 months after valve replacement. There was no early or late death among the 3 patients who underwent aortic root replacement. Actuarial late survival was 85.7% at 10 years and 77.1% at 15 years (Fig 3).

Reoperation

Reoperation was necessary in 5 patients (16%). The pulmonary autograft in the aortic position was replaced in 4 patients, 1 of whom also required replacement of the homograft valve in the pulmonary position. In the fifth patient, reoperation was performed to remove an aortic homograft that had undergone obstructive degeneration in the right ventricular outflow tract. The causes of reoperation on the pulmonary autograft were culture-proven bacterial endocarditis in 3 patients and probable endocarditis in the fourth, who had perforation of one valve cusp. In 3 patients, the valve was replaced with an aortic homograft, whereas in the fourth patient, who had an excavating root abscess burrowing into the septum, the autograft was replaced with a homograft aortic root. The pulmonary autograft in this case was entirely normal with

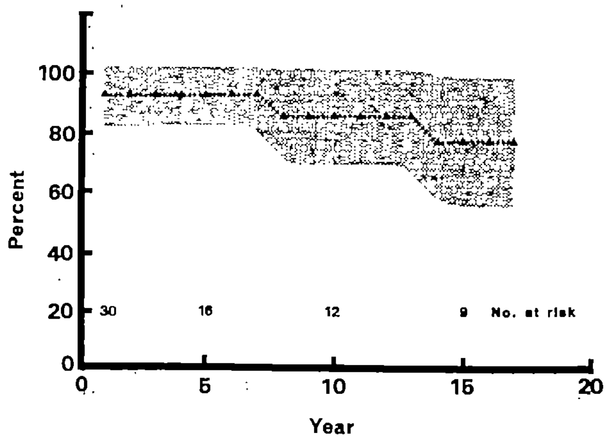

Fig 3. Linearized actuarial survival after aortic valve or root replacement with the pulmonary autograft. Shaded area *represents the 95% confidence interval.*

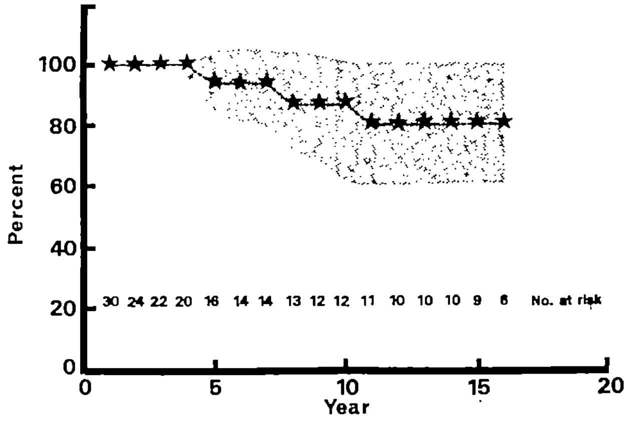

Fig 5. Actuarial freedom from reoperation and 95% confidence interval (shaded area*) for homograft valves in the right ventricular outflow tract.*

no calcification and only slight thickening of the cusps 10 years after implantation. All patients survived reoperation.

With respect to the pulmonary autograft, the actuarial rate of freedom from reoperation was 74% ± 11% at 16 years (Fig 4), whereas the actuarial rate of freedom from reoperation on the right ventricular outflow tract was 80% ± 10% (Fig 5). Conversely, the incidence of reoperation was 1.8% per patient-year for the left ventricular outflow tract and 1.4% per patient-year for the right ventricular outflow tract. It is difficult to assess the actuarial rates of freedom for both valves because this becomes a double-valve replacement with dissimilar valves, according to the concept of valve failure described by Edmunds and associates [11].

Bacterial Endocarditis

Infection involved the pulmonary autograft in 4 patients, 4 (2 patients), 8, and 10 years after implantation. In 1 patient, the homograft valve in the right ventricular outflow tract was infected also. All of these patients underwent successful reoperation. As endocarditis was the only reason for reoperation on the pulmonary autograft, its incidence also was 1.8% per patient-year and actuarial freedom from endocarditis, 74% ± 11% at 16 years (see Fig 4).

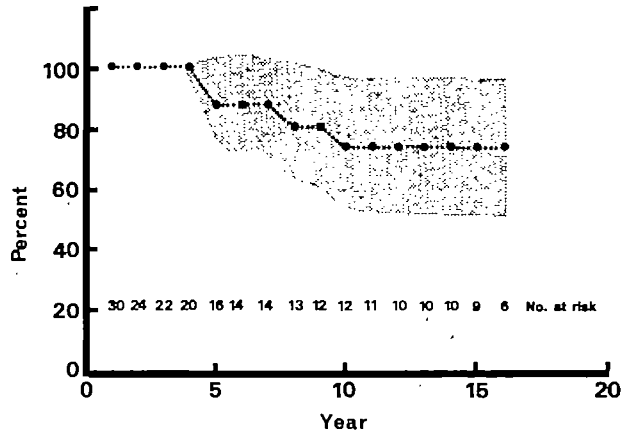

Fig 4. Actuarial freedom from endocarditis or reoperation on the pulmonary autograft in the left ventricular outflow tract. The 95% confidence interval is shown by the shaded area.

Thromboembolic Complications

No patient received anticoagulation and there were no thromboembolic episodes.

Pregnancy

During the follow-up period, 2 patients became pregnant and had uncomplicated deliveries of normal babies.

Late Functional Result

All survivors were in New York Heart Association functional class I at the time of follow-up and none was receiving any cardiac medication. Echocardiography, performed 3 weeks to 16 years postoperatively, detected no gradient across the left ventricular outflow tract. Mild regurgitation as demonstrated by Doppler examination of the autograft is common, but this has not been hemodynamically significant or progressive in the 18 patients studied to date (see Fig 2). There has been no evidence of calcification in the pulmonary autograft on either chest roentgenogram or echocardiographic examination. Actuarial survival and freedom from all valve-related complications was 55% ± 12% at 16 years (Fig 6).

Comment

Young patients who require replacement of the aortic valve continue to pose both technical and philosophical challenges in cardiac surgery. Although the importance of conserving left ventricular function is generally accepted [13], there often is a tendency to delay operation awaiting growth of the child, particularly when it is a secondary procedure. Other factors that also influence the timing of operation or the type of operation include the size of the

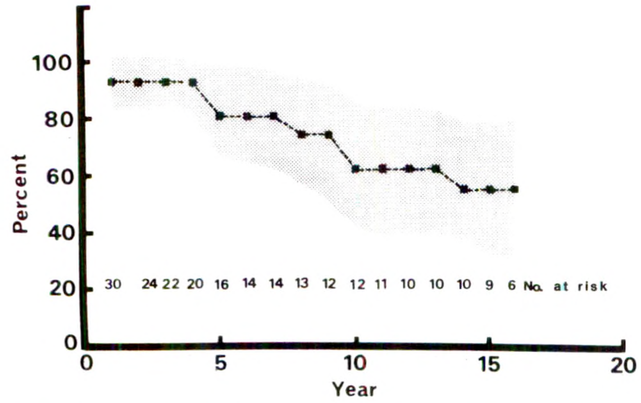

Fig 6. Actuarial freedom from all valve-related complications and late death, whether or not valve-related. Shaded area *indicates the 95% confidence interval.*

aortic annulus, the long life expectation of the patient, and social circumstances that may complicate the management of anticoagulation therapy.

After the initial enthusiasm for pericardial and porcine xenograft prostheses, which virtually obviated the need for anticoagulation, it became apparent that accelerated structural degeneration made these valves unsuitable for children, particularly on the left side of the heart [1–3]. It remains to be established whether recent modifications in the preservation of xenograft tissue will retard the rate of calcification enough to be clinically useful. But, at the present time, mechanical prostheses are widely regarded as the preferred alternative.

The low-profile bileaflet mechanical valves have good hemodynamic performance even in some of the smaller sizes [13–14], but their use is still complicated by thrombogenicity [14–16]. In children, they have been managed both with and without anticoagulation or platelet inhibitors [15]. Recent reviews, however, suggest that most patients with mechanical valves on the left side of the heart should receive anticoagulants [15]. This may prove difficult to manage in teenagers with poor medication compliance, young adults with variable alcohol consumption, female patients who wish to conceive children, or patients without easy access to medical supervision. Moreover, many patients with obstructive lesions have a small ventriculoarterial junction or tunnel type of left ventricular outflow tract. Several methods of annulus enlargement have been used to permit implantation of adequate-sized prostheses in children [17–19], but these still do not ensure that reoperation will not be necessary later in life.

The pulmonary autograft may offer a solution to some of these problems. From the point of view of the hemodynamic function and freedom from thromboembolic complications, it retains all the advantages of a homograft valve in the aortic position. In addition, because of its undoubted viability and compatibility, the autograft should be less prone to calcification and structural degeneration. It is noteworthy that these complications were not observed in any of our patients, as long as 16 years after operation.

The ability of the pulmonary valve to withstand systemic pressures has been questioned in view of the incompetence that often accompanies long-standing pulmonary hypertension and the occurrence of aneurysms in pulmonary homografts used for right ventricular outflow replacement. Experimental studies have demonstrated that the pulmonary valve cusps have about three times more tensile strength than aortic valve cusps and that distensibility of the pulmonary autograft in the aortic root is limited [20]. There is thus no hemodynamic or biomechanical reason why the autograft should not function perfectly in the systemic circulation, and this has been confirmed by the absence of serious or progressive valve incompetence among our patients.

The only cause of valve failure in this series was bacterial endocarditis, and its relatively high incidence in young patients gives cause for concern. Aortic homografts in the left ventricular outflow tract also have been noted to become infected in about 6% of patients, the highest incidence occurring within 2 years of implantation [21, 22]. The pulmonary autograft, in contrast, tended to be affected about twice as often but only after about 4 years in both children and older patients [5, 6], suggesting a different underlying pathogenesis. There is not any obvious reason why endocarditis should occur more frequently on the pulmonary autograft than on aortic homografts in the left ventricular outflow tract, although many of the patients in this series required valve replacement for endocarditis in the first instance and thus may have been at greater risk of reinfection. Certainly, the need for careful antibiotic prophylaxis in this group of patients is emphasized.

Reconstruction of the right ventricular outflow tract proved to be comparatively uncomplicated, both at the time of removing the autograft and subsequently to replace infected or degenerate homografts. Initially, an aortic homograft valve was implanted, but we now prefer to insert a pulmonary homograft in the orthotopic position. This valve has a better geometrical fit into the right ventricular outflow tract and from experimental studies [23] should be less likely to calcify, thus delaying reoperation and realizing the excellent long-term results of homografts on the right side of the heart [24].

The relatively high operative mortality in the early part of this series was related to the learning curve of the pulmonary autograft operation, specifically the importance of coronary artery branches in proximity to the pulmonary valve [7]. Three of the four operative deaths probably resulted from damage to the first septal branch of the left anterior descending coronary artery during dissection of the pulmonary autograft. With better understanding of the coronary anatomy, it has been possible to avoid this complication, and all children operated on since 1971 have survived operation.

It is of interest that the very small group of 3 patients who underwent aortic root replacement with the pulmonary autograft experienced neither early nor late mortality or morbidity. This may be due to the fact that root replacement achieves better relief of left ventricular outflow obstruction and retains a geometrically perfect valve with its own intact leaflets and sinuses. However, the follow-up of these patients is still less than 2 years and cautions against firm conclusions at the present time.

Because it is living autogenous tissue, the patient's own pulmonary valve may have growth potential, particularly when it is used for complete aortic root replacement. Although no outflow gradient developed in any patient in this series, most patients were well-grown at the time of operation and the larger diameter of the normal pulmonary valve that was transferred to the aortic position might be expected to accommodate an increasing cardiac output. In a limited number of patients it was possible to assess enlargement of the pulmonary autograft in the aortic root by echocardiography (see Table 1), and this suggested that growth potential may be realized postoperatively in young patients. Should this prove to be substantiated in a larger group, permanent relief of left ventricular outflow tract obstruction might become possible at any age. This technique would then be especially useful in the growing number of patients who survive valvotomy for critical aortic stenosis or repair of interrupted aortic arch during infancy but return with multiple-level outflow obstruction early in childhood.

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Failure of Hancock Pericardial Xenografts: Is Prophylactic Bioprosthetic Replacement Justified?

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The incidence of major valve-related complications was evaluated in a series of patients in whom the Hancock pericardial xenograft was used for aortic (AVR; n = 84), mitral (MVR; n = 17) and mitral-aortic (MAVR; n = 13) valve replacement. At 7 years actuarial survival is 66% ± 8% after AVR, 64% ± 13% after MVR, and 41% ± 15% after MAVR, whereas actuarial freedom from valve-related death is 79% ± 7% after AVR, 78% ± 13% after MVR, and 81% ± 12% after MAVR. Actuarial freedom from thromboemboli and anticoagulant-related hemorrhage at 7 years is 93% ± 4% and 98% ± 2% after AVR and 83% ± 10% and 88% ± 11% after MVR; no such complications occurred after MAVR. Structural valve deterioration determined at reoperation, at autopsy, or by clinical investigation was observed in 34 patients with AVR (10.0 ± 0.2%/patient-year), in 10 with MVR (10.6 ± 3.3%/patient-year), and in 9 with MAVR (16.6 ± 5.5%/patient-year). After AVR, 19 patients underwent reoperation and 2 died before reoperation; 4 patients with MVR underwent reoperation, and 7 patients with MAVR underwent reoperation and 1 died before reoperation. Seventy-eight percent of the current survivors (13 patients with AVR, 7 with MVR, and 1 with MAVR) have clinical evidence of valve failure. At 7 years actuarial freedom from structural deterioration of the Hancock pericardial xenograft is 25% ± 7% after AVR, 29% ± 14% after MVR, and 0% after MAVR. The extremely poor durability of the Hancock pericardial xenograft, besides confirming the need for a closer noninvasive monitoring of Hancock pericardial xenograft recipients, justifies prophylactic replacement of this device in asymptomatic patients with clinical evidence of Hancock pericardial xenograft dysfunction.

(Ann Thorac Surg 1991;51:430–7)

Bioprostheses made of bovine pericardium, introduced as an alternative to porcine valves in 1970 [1], have shown an extremely high incidence of early mechanical failures, responsible for their limited durability [2–6].

For editorial comment, see page 357.

These results, together with the observation that dysfunction of pericardial xenografts can occur suddenly [7, 8], have suggested the need for a periodical follow-up of recipients of such devices and possibly elective reoperation in asymptomatic patients with clinical evidence of valve failure [4]. Patients receiving a Hancock pericardial xenograft (HPX) at our institution were therefore reevaluated mainly to assess the incidence of structural deterioration and to establish the most proper method of management of long-term survivors.

Material and Methods

A total of 97 HPXs were implanted in 84 patients during the interval from August 1981 to July 1984. There were 48 male and 36 female patients with a mean age of 55.7 ± 13 years (range, 13 to 75 years). Aortic valve replacement (AVR) was performed in 54 patients, mitral valve replacement (MVR) in 17, and combined mitral and aortic valve replacement (MAVR) in 13. The preoperative clinical characteristics of this patient population and the indications for valve replacement, as well as previous operations and associated surgical procedures, are summarized in Table 1.

Operative techniques and anticoagulant policy in HPX recipients have been previously reported [4, 6]. Particularly, patients with AVR were usually not anticoagulated or received oral anticoagulants only for the first 3 months. Patients with atrial fibrillation were indefinitely anticoagulated after MVR and MAVR in the presence of a large left atrium or left atrial thrombosis.

Patients discharged were reevaluated mostly by direct visit during a 6-month period ending in December 1989. All long-term survivors were scheduled for a two-dimensional transthoracic echocardiographic study on a biannual basis or whenever required by a change of clinical status. Criteria to define and evaluate valve-related complications are those recently recommended [9]. Linearized rates, expressed as percent per patient year (%/pt-y), are calculated for any of such complications, and

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Table 1. Summary of Preoperative Clinical Characteristics

Variable	AVR	MVR	MAVR
No. of patients	54	17	13
Male/female	33/21	5/12	10/3
Mean age (y)	55 ± 13	53 ± 12	58 ± 10
Age range (y)	13–73	22–70	38–75
Preoperative functional class			
NYHA II	1	. . .	. . .
NYHA III	40	15	7
NYHA IV	13	2	6
Cause of valvar disease			
Rheumatic	16	8	6
Calcific degeneration	18	. . .	. . .
Myxoid degeneration	7	3	4
Ischemic	. . .	1	. . .
Endocarditis	6	. . .	. . .
Congenital	1	. . .	. . .
Prosthesis failure	6	5	3
Cardiac rhythm			
Sinus	45	2	4
Chronic atrial fibrillation	9	15	9
Previous procedures			
AVR	6	2	3
MVR	. . .	5	2
Mitral valvoplasty	3	3	1
Coartectomy	1	. . .	. . .
Associated procedures			
MVR[a]	10	. . .	. . .
Mitral valvoplasty	2	. . .	. . .
Tricuspid valvoplasty	. . .	1	. . .
CABG	7	1	1

[a] With other bioprostheses (Hancock porcine in 8 and Liotta in 2).

AVR = aortic valve replacement; CABG = coronary artery bypass graft; MAVR = mitral-aortic valve replacement; MVR = mitral valve replacement; NYHA = New York Heart Association.

freedom from major postoperative events is expressed in actuarial fashion, including in all actuarial curves the operative mortality. Continuous data are presented as mean ± 1 standard error of the mean and categorical data as percent with the 70% confidence limits (CL).

Hancock pericardial xenografts explanted at reoperation or recovered at autopsy were studied with gross, microradiographic, histological, and ultrastructural investigations. Details of the results of a morphological study of HPX explants have been reported elsewhere [10].

Results

Early and Late Mortality

There were eight hospital deaths: 4 patients died after AVR (7.4%; 70% CL, 3.7% to 13.0%), 1 after MVR (5.8%; 70% CL, 0.7% to 18.6%), and 3 after MAVR (23%; 70% CL, 10.4% to 41.0%) (Table 2). The causes of death were the following: low output state in 4 patients after AVR, intraoperative cerebral damage in 1 patient after MVR, postoperative hemorrhage in 2 patients after MAVR, and low output syndrome in 1 patient after MAVR. None of the early deaths was valve-related.

In the entire series total follow-up is 452 pt-y; cumulative duration of follow-up is 304 pt-y after AVR (range, 0.4 to 8.3 years; mean, 5.9 ± 1.6 years); 94 pt-y after MVR (range, 0.6 to 8.3 years; mean, 5.8 ± 2.1 years), and 54 pt-y after MAVR (range, 0.9 to 8.0 years; mean, 5.4 ± 2.1 years). Follow-up is 100% complete in the entire series.

Of the 76 patients discharged 21 died in the late postoperative period. There were 12 late deaths after AVR (3.9 ± 1.1%/pt-y), 4 after MVR (4.2 ± 2.1%/pt-y), and 5 after MAVR (9.2 ± 4.1%/pt-y). The causes of late death are shown in Table 3. Actuarial survival at 7 years is 66% ± 8% after AVR, 64% ± 13% after MVR, and 41% ± 15% after MAVR (Fig 1).

Currently, 27 patients are alive with their original HPX in place: 18 with AVR, 8 with MVR, and 1 with MAVR; 13 are in functional class I, 9 in class II, and 5 in class III.

Table 2. Summary of Major Postoperative Complications

	AVR		MVR		MAVR	
Complication	No.	%/pt-y	No.	%/pt-y	No.	%/pt-y
Late death	12	3.9 ± 1.1	4	4.2 ± 2.1	5	9.2 ± 4.1
Valve-related death	8	2.6 ± 0.1	2	2.1 ± 1.5	2	3.7 ± 2.6
Thromboembolism	3	0.1 ± 0.1	3	3.2 ± 1.8	. . .	. . .
Fatal	1	0.03 ± 0.03	1	1.0 ± 1.0	. . .	. . .
Anticoagulant-related hemorrhage	2	0.6 ± 0.4	1	1.0 ± 1.0	. . .	. . .
Fatal	1	0.03 ± 0.03	. . .	. . .	. . .	. . .
Endocarditis	6	2.0 ± 0.7	1	1.0 ± 1.0	. . .	. . .
Paraprosthetic leak	1	0.03 ± 0.03	. . .	. . .	. . .	. . .
Reoperation	23	7.5 ± 1.6	4	4.2 ± 2.1	7	13.0 ± 5.0
Structural deterioration[a]	34	10.0 ± 0.2	10	10.6 ± 3.3	9	16.6 ± 5.5

[a] Determined at reoperation, autopsy, or clinical investigation.

AVR = aortic valve replacement; MAVR = mitral-aortic valve replacement; MVR = mitral valve replacement.

Table 3. Causes of Late Death

Cause	AVR	MVR	MAVR
Cardiac	2	1	2
Valve-related			
Endocarditis	2	. . .	. . .
Structural deterioration	2	. . .	1
Reoperation	2	. . .	1
Thromboembolism	1	1	. . .
Anticoagulant-related hemorrhages	1	. . .	. . .
Sudden, unexplained	. . .	1	. . .
Malignancy	1	1	1
Unknown	1	. . .	. . .
Total	12	4	5

AVR = aortic valve replacement; MAVR = mitral-aortic valve replacement; MVR = mitral valve replacement.

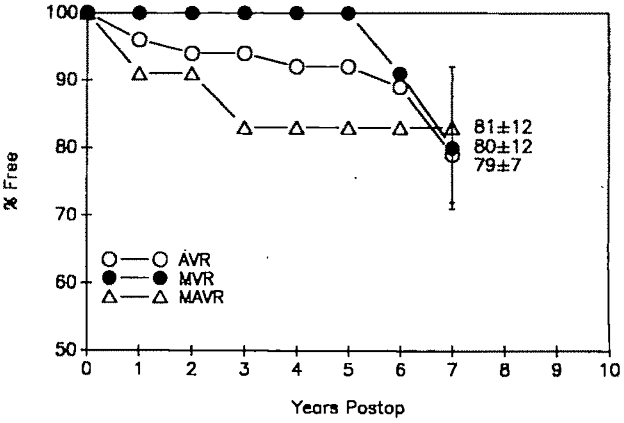

Fig 2. Actuarial freedom from valve-related death. (Abbreviations as in Fig 1.)

There were eight valve-related deaths in the AVR group (2.6 ± 0.1%/pt-y), because of endocarditis in 2 patients, at reoperation for HPX structural deterioration in 2, because of HPX structural deterioration without reoperation in 2, because of cerebral embolism in 1, and because of gastric hemorrhage in 1. There were two valve-related deaths after MVR (2.1 ± 1.5%/pt-y), due to cerebral embolism in 1 and sudden, unexplained death in the other. Finally, there were two valve-related deaths among patients with MAVR (3.7 ± 2.6%/pt-y): 1 patient died of low output syndrome at reoperation because of structural failure of both HPXs and 1 died at home because of failure of both HPXs proved at autopsy. Actuarial freedom from valve-related deaths at 7 years is 79% ± 7% after AVR, 80% ± 12% after MVR, and 81% ± 12% after MAVR (Fig 2).

Thromboembolic Complications

Thromboembolic complications occurred in 3 patients with AVR (0.1 ± 0.1%/pt-y). Of these 2, who were not anticoagulated, had a cerebral embolism after 20 and 28 months, respectively, both of which resolved without sequelae; the third patient, who had also a porcine valve in the mitral position and was anticoagulated, sustained a fatal cerebral embolism after 22 months. Two patients had embolic complications after MVR (3.2 ± 1.8%/pt-y): 1 of them, who was not anticoagulated, had a cerebral embolism after 4 years with permanent hemiparesis and the other, while still on anticoagulants, had two episodes of peripheral embolism 14 months and 5 years after MVR; the last one, causing acute occlusion of the aortic bifurcation, required emergency embolectomy with subsequent death due to acute renal failure. No thromboembolic complications were observed in patients with MAVR. Actuarial freedom from thromboemboli at 7 years is 93% = 4% after AVR, 83% ± 10% after MVR, and 100% after MAVR (Fig 3).

Anticoagulant-Related Hemorrhage

Major hemorrhagic complications were observed in 3 patients, 2 with AVR (0.6 ± 0.4%/pt-y) and 1 with MVR (1.0 ± 1.0%/pt-y). Two patients had gastric bleeding 1 and 2 months after AVR, and 1 of these patients died; both

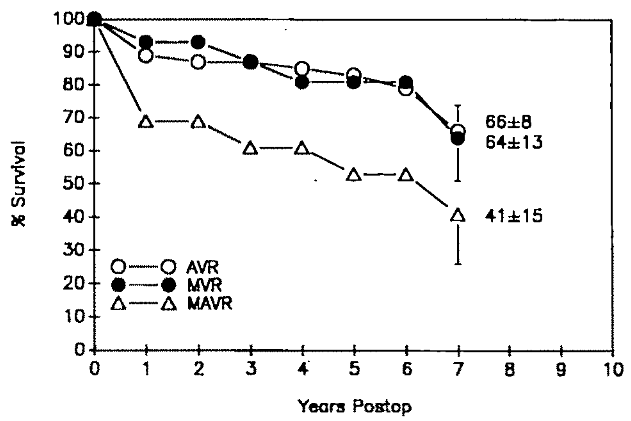

Fig 1. Actuarial survival after isolated aortic (AVR), mitral (MVR), and mitral-aortic (MAVR) valve replacement with the Hancock pericardial xenograft.

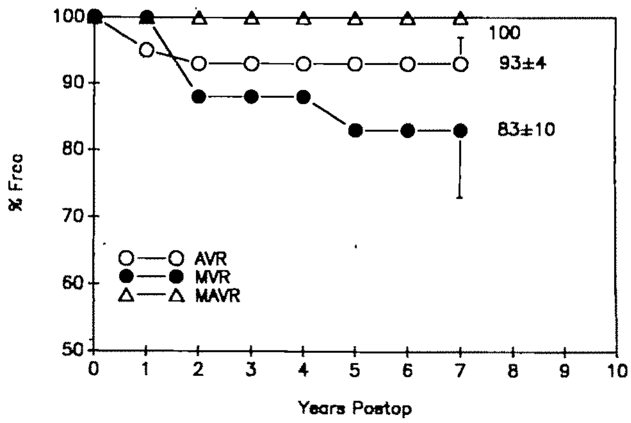

Fig 3. Actuarial freedom from thromboembolic complications. (Abbreviations as in Fig 1.)

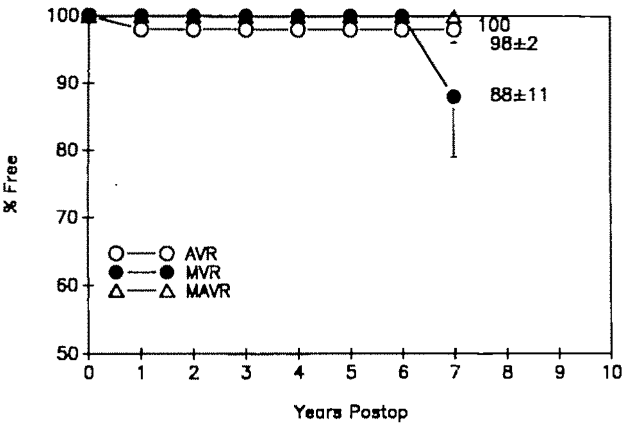

Fig 4. Actuarial freedom from hemorrhage related to chronic anticoagulation. (Abbreviations as in Fig 1.)

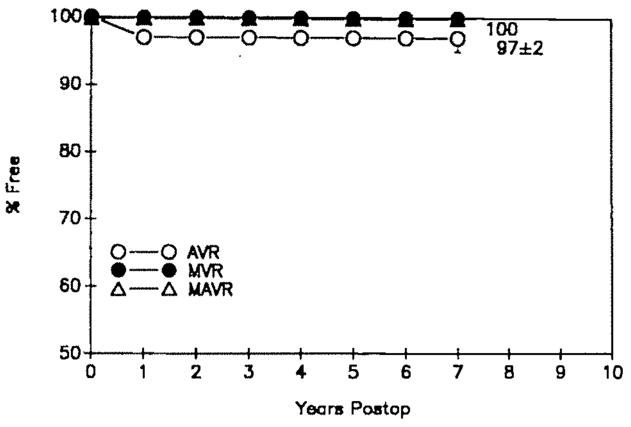

Fig 6. Actuarial freedom from paraprosthetic leak. (Abbreviations as in Fig 1.)

patients were still on anticoagulants. One patient with MVR had a nonfatal gastrointestinal hemorrhage after 6 years. Actuarial freedom from anticoagulant-related hemorrhages at 7 years is 98% ± 2% after AVR, 88% ± 11% after MVR, and 100% after MAVR (Fig 4).

Endocarditis

Endocarditis involved 6 patients with AVR (2.0 ± 0.7%/pt-y) and 1 with MVR (1.0 ± 1.0%/pt-y). Of the AVR patients 3 underwent successful reoperation after 7, 29, and 47 months, respectively; 2 died without reoperation and 1 was apparently cured with medical treatment. One patient with MVR underwent reoperation successfully after 24 months. Actuarial freedom from endocarditis at 7 years is 85% ± 7% after AVR, 93% ± 6% after MVR, and 100% after MAVR (Fig 5).

Paraprosthetic Leak

Paraprosthetic leak was observed only in 1 patient with AVR (0.03 ± 0.03%/pt-y), who underwent successful HPX replacement after 16 months. Actuarial freedom from this complication at 7 years is 97% ± 2% after AVR and 100% after MVR and MAVR (Fig 6).

Reoperation

A total of 34 patients required reoperation during the follow-up period. Reoperation was performed in 23 after AVR (7.5 ± 1.6%/pt-y), because of paraprosthetic leak in 1 and endocarditis in 3 without deaths, and because of structural deterioration in 19 with 2 deaths (10.5%; 70% CL, 3.5% to 23.2%); of the latter, 1 had emergency reoperation because of acute onset of HPX regurgitation and 1 died at his second reoperation. Four patients underwent reoperation after MVR, 1 because of endocarditis and 3 because of structural deterioration without deaths. Finally, 7 patients with MAVR underwent reoperation because of structural deterioration of the aortic (4 patients), mitral (1 patient), or both HPXs (2 patients) with one death (14.3%; 70% CL, 1.8% to 40.6%). However, in all patients but 1 both HPXs were explanted, replacing simultaneously also the one that appeared grossly normal. Actuarial freedom from reoperation for all

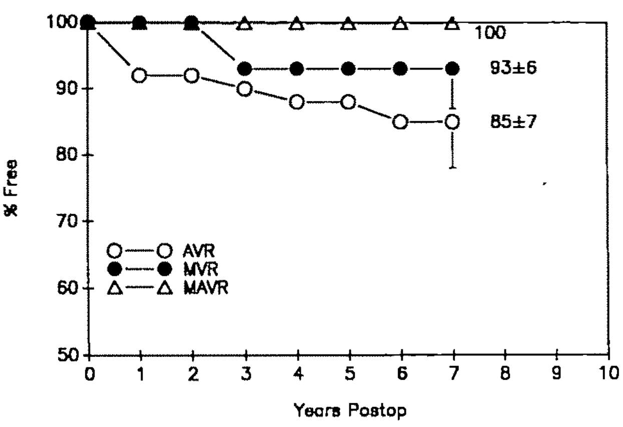

Fig 5. Actuarial freedom from prosthetic valve endocarditis. (Abbreviations as in Fig 1.)

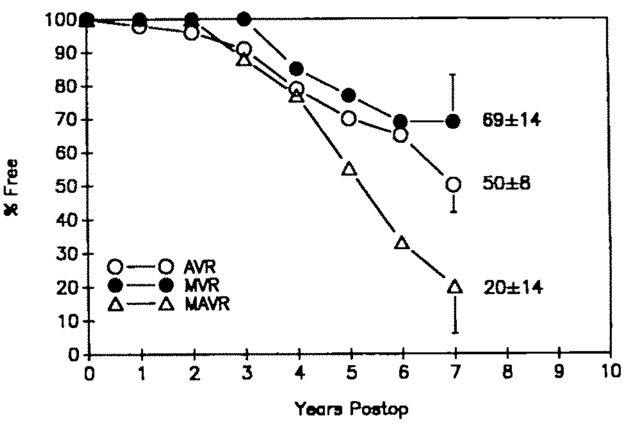

Fig 7. Actuarial freedom from reoperation due to all causes. (Abbreviations as in Fig 1.)

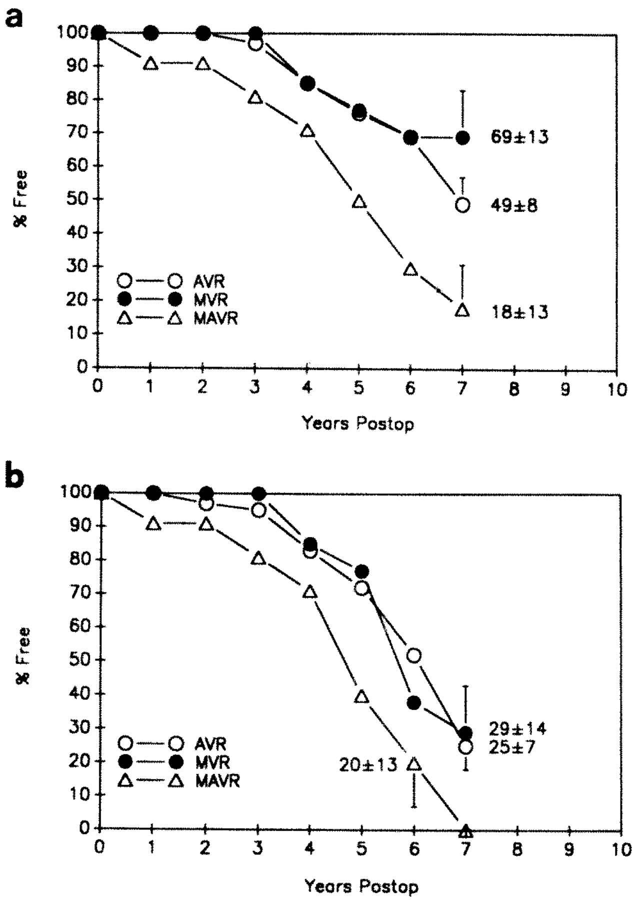

Fig 8. (a) Actuarial freedom from prosthesis structural deterioration requiring reoperation or causing death. (b) Actuarial freedom from structural deterioration determined at reoperation, autopsy, or clinical investigation. (Abbreviations as in Fig 1.)

causes at 7 years is 50% ± 8% after AVR, 69% ± 14% after MVR, and 20% ± 14% after MAVR (Fig 7).

Structural Deterioration

A total of 32 patients underwent reoperation or died because of HPX structural deterioration, 21 after AVR (7.0 ± 1.5%/pt-y), 3 after MVR (3.1 ± 1.8%/pt-y), and 8 after MAVR (14.8 ± 5.2%/pt-y). After AVR 19 patients underwent reoperation and 2 died without reoperation after a mean interval of 5.0 ± 1.4 years (range, 2.9 to 7.7 years). All patients with MVR underwent reoperation after a mean interval of 4.2 ± 0.9 years (range, 3.2 to 5.1 years). After MAVR 7 patients underwent reoperation and 1 died without reoperation after a mean interval of 4.6 ± 1.3 years (range, 2.8 to 6.5 years).

In 21 (78%) of the current survivors, 13 with AVR, 7 with MVR, and 1 with MAVR, clinical and echocardiographic signs of HPX dysfunction have been documented at a mean of 5.8 ± 1.5 years after operation (range, 1.8 to 7.9 years), with predominant incompetence in 87% and stenosis in 13%. Including these patients the overall linearized incidence of HPX structural deterioration is 10.0 ± 0.2%/pt-y after AVR, 10.6 ± 3.3%/pt-y after MVR, and 16.6 ± 5.5%/pt-y after MAVR. At 7 years, actuarial freedom from structural deterioration causing reoperation or death is 49% ± 8% after AVR, 69% ± 13% after MVR, and 18% ± 13% after MAVR (Fig 8a); actuarial freedom from structural deterioration, determined by reoperation, autopsy, or clinical investigation, is 25% ± 7% after AVR, 29% ± 14% after MVR, and 0% after MAVR (Fig 8b).

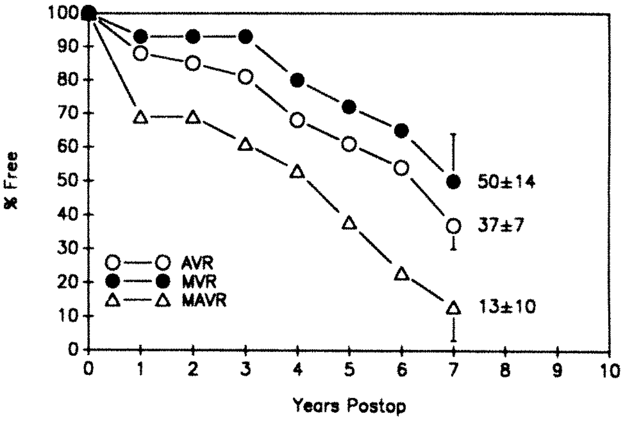

Fig 9. Actuarial freedom from valve-related death and reoperation. (Abbreviations as in Fig 1.)

Overall Valve Performance

Actuarial freedom from valve-related death and reoperation at 7 years is 37% ± 7% after AVR, 50% ± 14% after MVR, and 13% ± 10% after MAVR (Fig 9). Actuarial freedom from valve-related death and permanent disability at 7 years is 73% ± 7% after AVR, 74% ± 13% after MVR, and 61% ± 13% after MAVR (Fig 10). Actuarial freedom from valve-related death and morbidity at 7 years is 14% ± 6% after AVR, 7% ± 7% after MVR, and 0% after MAVR (Fig 11).

Morphology of Hancock Pericardial Xenograft Explants

The typical morphological substrates of HPX failure have been described in detail previously [10]. Briefly, most of the explants removed because of structural deterioration

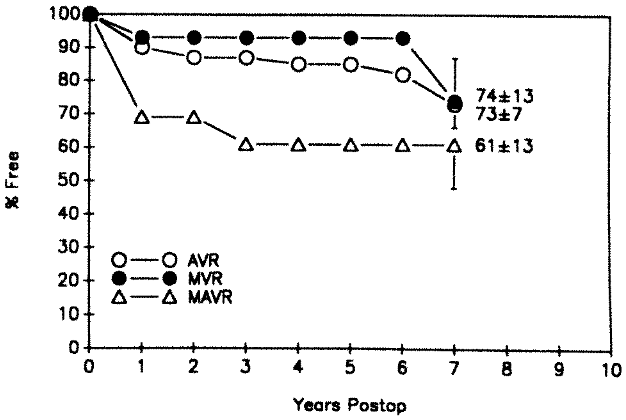

Fig 10. Actuarial freedom from valve-related death and permanent disability. (Abbreviations as in Fig 1.)

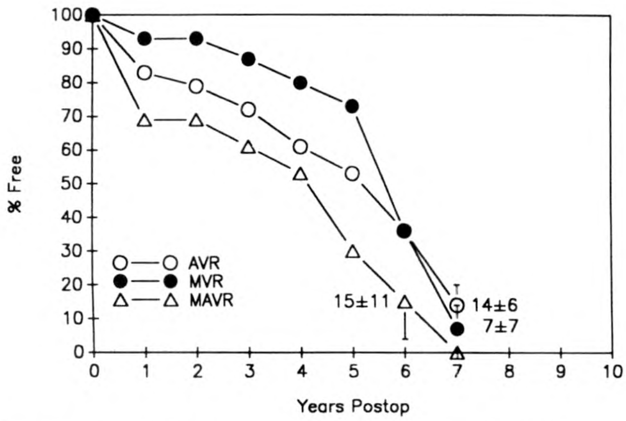

Fig 11. Actuarial freedom from valve-related death and morbidity. (Abbreviations as in Fig 1.)

showed tears of one or more cusps starting at the commissures and extending downward causing cusp prolapse and various degrees of regurgitation (Figs 12, 13); valve incompetence was the predominant mode of failure in more than 80% of explants studied and it was similar for HPXs implanted in mitral and aortic position. With the exception of infected valves, which showed severe calcific deposits, calcification was absent in most HPXs explanted for structural deterioration.

Comment

Biological prostheses have been extensively employed in the past, mainly to overcome the problems related to the use of mechanical devices, such as thromboembolic complications or hemorrhage related to the indefinite use of anticoagulants, which is mandatory in patients with mechanical prostheses but may be avoidable in many of those with tissue valves [11–13].

Bioprostheses manufactured with bovine pericardium have gained worldwide acceptance particularly because they combine the biocompatibility of biological tissue with a superior hemodynamic performance, when compared with porcine valves [14]. However, despite this advantage, there have been reports that, with increasing frequency, have called attention to the high incidence of early failures of pericardial xenografts. Gabbay and colleagues [2], in 1984, demonstrated the similarity between the lesions observed in Ionescu-Shiley pericardial xenografts and those noted in the same valves removed from a fatigue test system, showing also a poor durability of this device within 6 years after clinical MVR [3]. The same conclusions were reached by other groups, including ourselves, who experienced a high incidence of early failures of pericardial xenografts, either Ionescu-Shiley or Hancock, regardless of the site of valve implantation [4, 6, 15, 16].

Morphological studies have demonstrated that pericardial xenografts fail mostly because of cusp laceration, unlike porcine bioprostheses, in which structural deterioration is almost exclusively caused by tissue mineralization [17]. Cusp tears in pericardial xenografts are almost never calcium-related; they usually start at the commissures and are the result of the continuous bending stress or tissue abrasion on the Dacron cloth that covers the prosthetic stent [2, 10]. Repeated observations on surgical or autopsy specimens have conclusively shown that such mode of failure is typical of these devices, appears highly predictable, and is clearly related to a faulty prosthetic design [2, 5, 10, 18, 19]. Furthermore, small cusp rupture, which may initially cause only trivial prosthetic regurgitation, may acutely progress, seriously jeopardizing patient survival [7, 8].

We [6] have previously reported our medium-term

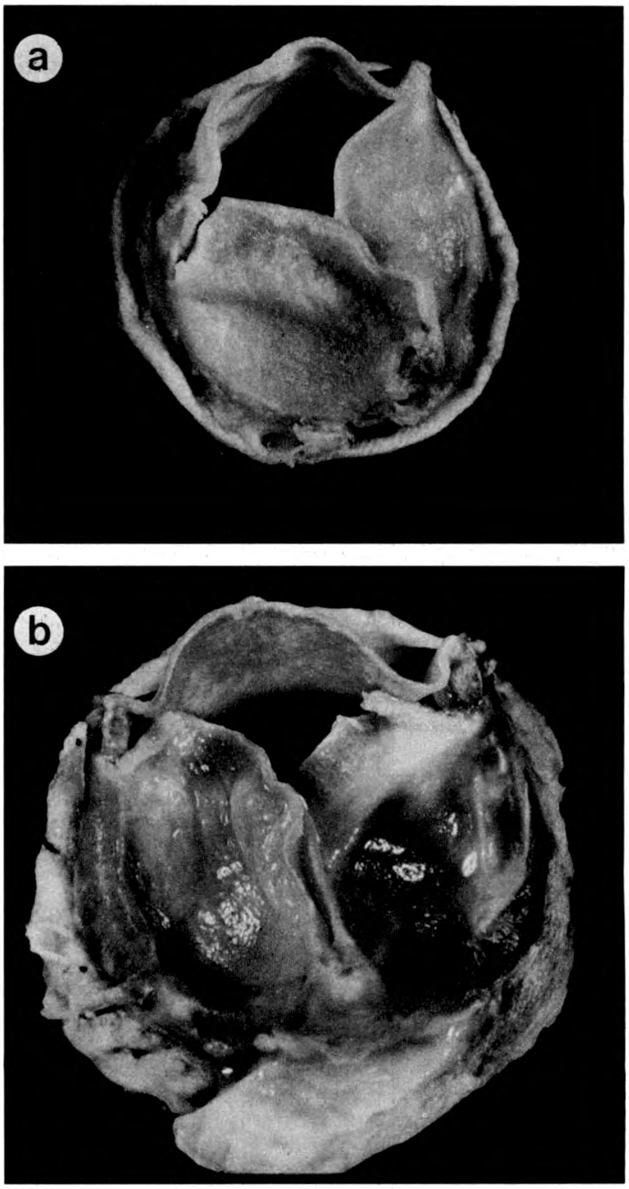

Fig 12. Gross view of an aortic (a) and a mitral (b) Hancock pericardial xenograft explanted from 2 different patients because of severe regurgitation after 75 and 58 months, respectively. Both explants showed typical features of pericardial valve failure represented by cusp tears starting at the commissural level.

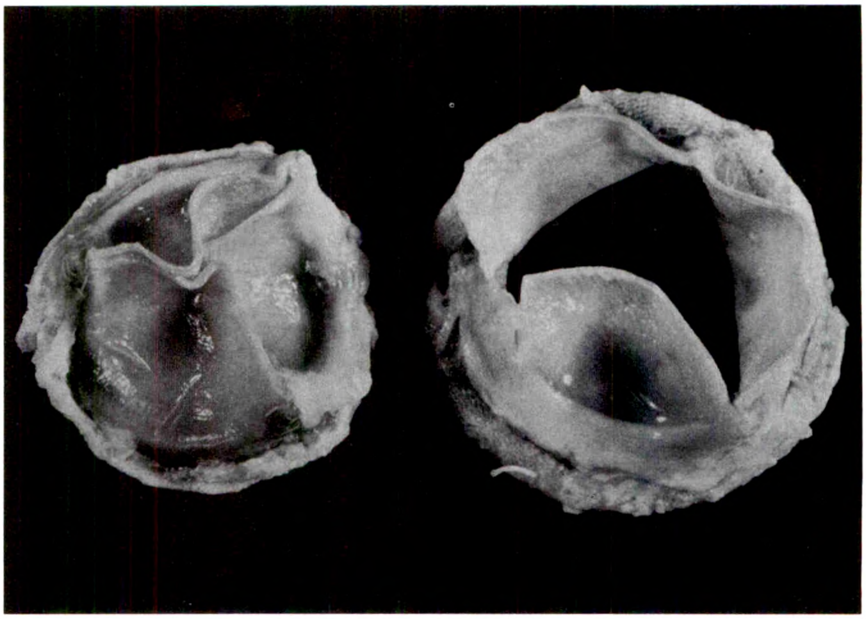

Fig 13. View of an aortic (left) and a mitral (right) Hancock pericardial xenograft explanted from the same patient after 72 months. The mitral valve showed tears at two commissures causing severe incompetence; the aortic valve, which appeared grossly normal, was replaced prophylactically.

results with the HPX in a limited series of patients in whom this device was used as alternative to the Hancock porcine bioprosthesis, the latter having been the tissue valve of choice in our center for almost two decades [20]. The purpose of this study was to assess the real incidence of structural deterioration of HPX at a longer follow-up, and to determine whether asymptomatic HPX recipients with or without clinical evidence of valve failure should undergo a planned, prophylactic HPX replacement.

Reevaluation of patients with an HPX have confirmed the extremely poor durability of this device at 7 years, which still cannot be considered a long-term postoperative interval, as indicated by the high incidence of structural deterioration particularly after AVR and MAVR. Moreover, if we gather all cases of HPX structural deterioration observed at reoperation or autopsy with those determined at clinical investigation, as currently recommended [9], only 25% of patients with AVR, 29% of those with MVR, and none of those with MAVR are free from this complication at 7 years. These results, together with the morphological reports from our and other groups [10, 18, 19], confirm that bioprostheses obtained by individually sewing to a stent three separate leaflets of pericardium did not provide a durable valve substitute, as also witnessed by the retrieval from the market of some of these devices.

Transthoracic two-dimensional echocardiography, which allows frequent monitoring of prosthetic function, showed clear signs of valve failure in 78% of our current survivors with their original HPX still in place. Furthermore, 3 of our patients died because of HPX structural deterioration before reoperation could be performed, and in 1, sudden onset of massive aortic regurgitation prompted emergency, unsuccessful reoperation. Finally, in our experience reoperation for structural deterioration of bioprosthetic valves, when performed on an elective basis, is associated with an acceptable risk [21, 22].

In our opinion, all these considerations not only strongly support the need for a continuous and closer reevaluation of HPX recipients by noninvasive methods, but also justify an early prophylactic replacement of an HPX even in asymptomatic patients with only initial signs of prosthetic failure who, therefore, should be scheduled for an elective reoperation.

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Management of Aortic Insufficiency in Chronic Aortic Dissection

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From January 1980 to December 1988, 44 patients with chronic aortic dissection and aortic insufficiency underwent operation. This group of patients was analyzed to evaluate the outcome of those in whom the aortic valve was preserved compared with those having valve replacement. The overall preoperative characteristics of the two groups were similar except for the incidence of Marfan's syndrome. Valve replacement was the elected procedure in patients with valve degeneration or annuloaortic ectasia. In patients with leaflet prolapse with or without an enlarged annulus, a plastic procedure was used. In 48% of the patients, it was possible to preserve the valve. There were five hospital deaths (11%): three were due to low-output syndrome, one was due to bleeding, and one was due to neurological complications. There were two late deaths (5%). Follow-up of the 37 surviving patients ranged from 2 to 108 months (mean follow-up, 18 months). Seventy-eight percent of the survivors were in functional class I and the others were in class II. Two patients in whom the aortic valve was preserved had mild aortic insufficiency. Three patients with bioprostheses underwent reoperation because of prosthetic valve dysfunction. One patient who had aortoplasty and an aortic valve plastic procedure was seen with redissection and aortic insufficiency after 60 months and was reoperated on using the Bentall technique. The actuarial survival curves showed that patients who underwent valvoplasty had higher, but not significantly higher, survival rates than the valve replacement patients. We conclude the following: (1) valve resuspension is a satisfactory technique in patients with chronic dissection of the aorta, with a low mortality and fewer complications than valve replacement; (2) identification of the mechanism producing valvar insufficiency is fundamental to the choice of surgical procedure; and (3) aortoplasty should be avoided because of the high incidence of aortic redissection.

(Ann Thorac Surg 1991;51:438–42)

In acute dissections of the proximal aorta with valvar insufficiency, there is a marked tendency to preserve the aortic valve whenever the valve is not primarily involved [1–3]. In chronic dissections with aortic insufficiency, there is a tendency to replace the valve [1, 4–7]. In the early years of our experience [7], valve replacement was more frequently used, whereas now, preservation of the aortic valve is preferred. In this study, we analyze the outcome of patients with chronic aortic dissection with aortic insufficiency who underwent operation at our institution.

Material and Methods

Between January 1980 and December 1988, 128 patients with proximal aortic dissection underwent operation at our institution. Chronic aortic dissections were treated surgically in 62 patients, 44 (71%) of whom had aortic insufficiency. This group of 44 patients comprised 35 men and 36 whites. Age ranged from 23 to 66 years (mean age, 43 years) (Fig 1).

Arterial hypertension was present in 26 patients (59%) and Marfan's syndrome, in 7 (16%). The most frequent symptom was pain, present in 36 patients (82%). Cardiac failure was observed in 32 patients (73%). Aortic insufficiency was severe in 17 patients, moderate in 22, and mild in 5.

Chest radiography demonstrated an enlarged aorta in 37 patients (84%) and an enlarged cardiac silhouette in 32 (73%). A preoperative echocardiogram was obtained in 30 patients and showed aortic insufficiency in each. Cineangiograms demonstrated aortic insufficiency in all 44 patients; the dissection entrance was seen in 28 patients (64%), and associated coronary lesions were observed in 2 patients.

The dissection was a type I in 70% of the patients. In 5 patients, intraoperative echocardiography was useful in the dynamic identification of the valvar insufficiency. The incompetence was caused by annuloaortic ectasia, valve degeneration, or annulus enlargement with leaflet prolapse. In the first two situations, valve replacement was performed and in the third, the aortic valve was preserved.

In 41 patients (93%), the proximal aorta was substituted, and in the remaining 3, aortoplasty with a patch was performed. Preservation of the aortic valve using commissural resuspension was possible in 48% of the

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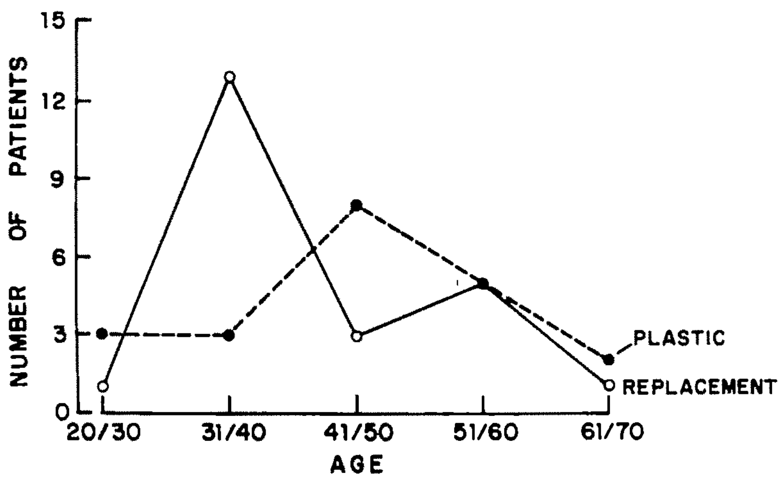


Fig 1. Comparison of age distribution between the two patient groups (aortic valve replacement versus valvoplasty). There is a significant difference between the groups for the category 31 through 40 years old. Most of the patients with Marfan's syndrome were in this group.

patients (Fig 2). In 16 of the 23 patients having valve replacement, the technique of Bentall and De Bono [8] was used; the other 7 underwent aortic valve replacement. In 5 of these 7, the dissection was corrected using a Dacron tube, and in 2, aortoplasty was performed. Six patients underwent associated surgical procedures: coronary artery bypass grafting in 3, reattachment of saphenous vein in 2, and mitral valve replacement in 1. In every patient operated on since 1986, biological glue was used. The false lumen was obliterated in every patient by suturing the aortic layers between two Teflon felt strips before inserting the Dacron tube.

Actuarial survival curves were obtained to compare the two groups of patients: those having aortic valve replacement and those having valvoplasty. Early death includes all deaths that occurred during operation, during hospitalization, or in the first 30 postoperative days.

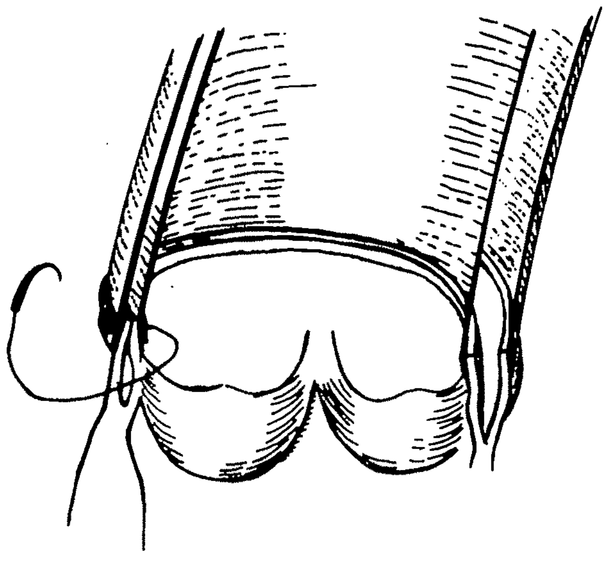


Fig 2. Resuspension of the valve is performed using two Teflon felt strips fixed with 4-0 Prolene continuous sutures and corrects the proximal dissection at the same time.

Nineteen patients had late evaluation by one or more of the following methods: echocardiography, digital angiography, conventional angiography, and computed tomography of the chest. Ten of these patients had had aortic valve replacement and 9, valvoplasty.

Statistical analysis was performed to compare discrete and continuous variables between the two patient groups. Discrete variables were compared with a χ^2 test or Fisher's exact test when necessary, and the continuous variables were analyzed by the Wilcoxon two-sample test (normal approximation). All late deaths were included in the actuarial calculation of survival.

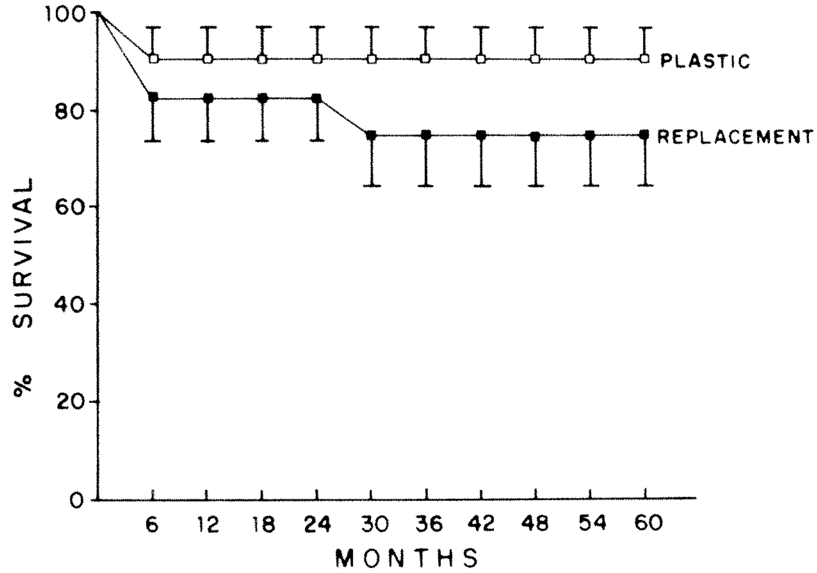
Results

Five patients (11%) died in the early postoperative period, and a postmortem examination of each was performed. Three patients had low-output syndrome, 1 died of bleeding, and 1 died of neurological complications. Two patients (5%) died late suddenly; postmortem examination was not done.

The 37 surviving patients were followed up from 2 to 108 months (mean follow-up, 18 months). Seventy-eight percent were in functional class I and the others were in class II. Among the 19 patients reevaluated by one or more of the methods mentioned previously, only 2 with preserved aortic valves had mild aortic insufficiency, and 2 had persistence of dissection at the descending aorta without clinical manifestations. We performed echocardiography on all patients with clinical signs of aortic insufficiency. Three patients with malfunctioning bioprostheses underwent reoperation using the Bentall-De Bono technique with metallic disc prostheses. One patient with prior aortoplasty and a valvoplastic procedure had redissection and aortic insufficiency 60 months after the initial operation; reoperation was performed using the Bentall technique.

The actuarial survival curves demonstrated that patients undergoing a valvoplastic procedure had a higher

Fig 3. Actuarial survival curves show that patients undergoing valvoplasty had a higher, but not significantly higher, survival rate than the valve replacement patients.



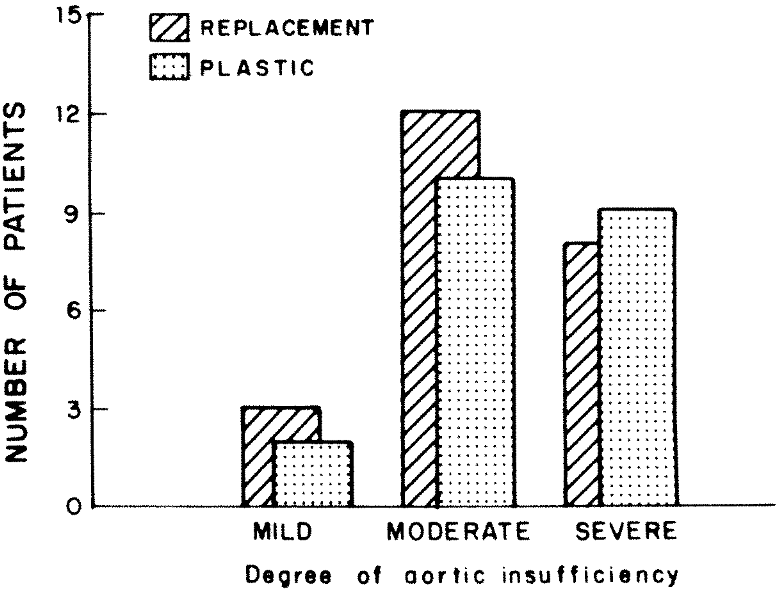
survival rate than the valve replacement patients, though the difference was not significant (Fig 3).

All 7 patients with Marfan's syndrome had valve replacement (Bentall-De Bono procedure), and that variable (Marfan's syndrome) was significant (valve replacement group versus valvoplasty group). No significant differences were found for other variables, including the degree of aortic insufficiency. Of the 5 patients with mild aortic insufficiency, 3 had valve replacement because of concomitant aortic stenosis or Marfan's syndrome (Fig 4).

Comment

Aortic dissections are classified as acute (up to 2 weeks after the initial episode) or chronic based on their duration [1]. Surgical treatment is accepted almost universally as the procedure of choice for chronic dissections of the aorta [4, 5, 7, 9–14]. Indications for operation include the development of symptoms clearly referable to the dissection or its complications, such as congestive heart failure secondary to aortic insufficiency, angina pectoris secondary to compromise of the coronary arteries, chest pain owing to saccular enlargement of the ascending aorta, transient ischemic attacks resulting from cerebrovascular insufficiency, or upper extremity ischemia. The second indication includes documented progressive enlargement of a saccular aneurysmal component of the ascending aorta. The third indication involves the presence of a saccular component that exceeds 100 mm in diameter, even in the absence of documented enlargement or symptoms [15, 16]. In the case of acute dissections, surgical treatment is indicated more frequently for those initiated in the proximal aorta [3–6, 12, 13, 17, 18].

Fig 4. Aortic valve replacements and plastic procedures were used in almost equal numbers in patients with similar degrees of aortic regurgitation.



Hospital mortality rates for surgical correction of chronic ascending aortic dissections range from 4% to 20% [3–5, 9, 12, 13]. Five-year survival is around 75% [11, 12, 19], and 10-year survival is 56% [11]. The mortality rate in our series [3] of patients with chronic proximal aortic dissection was 9%; resection of the primary rupture site was performed in 93% of these patients. Persistence of the dissection entrance orifice has no influence on the early results of surgical treatment [2]; however, it is an important risk factor in the long-term outcome [11]. The better results obtained with surgical treatment of chronic proximal aortic dissections are due to the low incidence of secondary complications [1–3]. The incidence of aortic insufficiency is 71% in our patients with chronic proximal dissection; in patients with acute dissection the incidence is about 55% [3]. Jex and colleagues [1] reported the incidence of aortic insufficiency to be 58% in patients with aortic dissection and 72% in those with chronic dissection, percentages similar to other reports in the literature [12]. Jex and associates attributed the higher incidence of aortic insufficiency in chronic dissections to natural selection and to the fact that diagnosis is easier in patients with clinical manifestations of valvar insufficiency.

The best treatment of aortic insufficiency in aortic dissection is debatable. In the acute phase, our group [3] preserved the aortic valve in 96% of patients with aortic insufficiency. Miller and colleagues [2] preserved it in 82% and Jex and co-workers [1], in 40%. Some authors [20, 21] have recommended aortic valve replacement for all cases of acute type A dissection, but others [1–3, 12] find that a philosophy of selective replacement of the aortic valve yields long-term function of the patient's natural valve without the additional long-term risk imposed by a prosthetic or bioprosthetic valve.

Miller and colleagues [12] discussed 32 surviving patients with acute type A dissections in whom the aortic valve was preserved. Two of these patients required aortic valve replacement 34 and 48 months postoperatively, and 2 others had asymptomatic mild aortic regurgitation. One of the 2 patients who required valve replacement had annuloaortic ectasia and, in retrospect, should have had concomitant valve replacement at the time of the initial operation [12]. Meng and co-workers [22] reported that 55 (92%) of 60 patients in a collected series were free from the need of valve replacement 2 to 10 years later. These results suggest that the durability of operative procedures that preserve the native valve in patients with acute type A dissection is satisfactory.

The mechanisms of aortic insufficiency in acute dissection include (1) a circumferential hematoma that widens the aortic root and separates the aortic cusps, (2) displacement of one cusp substantially below the level of the others by asymmetrical pressure of the dissecting hematoma, and (3) actual disruption of the support of the leaflet of the annulus, thus leading to a flail cusp. These mechanisms influence the ultimate therapy. In the case of the first two mechanisms, simple surgical decompression of the hematoma should allow full restoration of valvar competence. In the case of the third mechanism, however, an aortic valve prosthesis is required. We believe that in chronic aortic dissection, the mechanisms of aortic insufficiency are similar to those in the acute phase in many instances; accordingly the surgical treatment should be similar also. In the chronic phase, aortic insufficiency has not increased the surgical risk whatever the technique employed [1, 3–5, 9, 12].

Replacement of the aortic valve in the treatment of aortic insufficiency secondary to chronic dissection of the ascending aorta is more widely used (up to 100% of patients) than conservative procedures [2, 3, 5, 12]. In our early experience [7], the aortic valve was frequently replaced (78.3% of patients). However, with our increasing confidence in valvoplastic procedures [3], we have been trying to preserve the aortic valve in patients with chronic aortic dissection except those with annuloaortic ectasia, Marfan's syndrome, or primary valvar involvement. In patients with annuloaortic ectasia or Marfan's syndrome, we, like others [2, 8, 10, 23–26], use a valved conduit with reimplantation of the coronary arteries as described by Bentall and De Bono [8]. An alternative to direct reimplantation of the coronary arteries was presented by Cabrol and colleagues [27] and involves a tubular graft connected transversely to the Dacron tube and receiving the coronary ostia with end-to-end anastomoses. This technique has been used with good results [9, 19]. More recently, even those who usually do not favor valvoplasty in chronic aortic dissection with aortic insufficiency [1, 13] are tending to use these plastic procedures more frequently because of prosthetic valve complications. Jex and colleagues [1] reported better late results in patients with preserved aortic valves. Our experience leads to the same conclusion.

Aortoplasty, according to Jex and colleagues [1], was followed by aortic redissection in 31% of patients. We used this technique in only 3 patients. One (33%) of them was seen with late recurrence and had reoperation with the Bentall technique.

In conclusion, we believe the following:

1. Valve resuspension is a satisfactory technique in patients with chronic aortic dissection. It has a low mortality and a decreased incidence of complications compared with valve replacement.
2. Identification of the mechanism of valvar incompetence is fundamental to the choice of surgical procedure.
3. Aortoplastic procedures should be avoided because of the high incidence of redissection.

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Postcardiotomy Mechanical Circulatory Support in the Elderly

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The role of mechanical circulatory support after cardiac operations in elderly patients is not clearly established. Between November 1985 and July 1989, 18 patients 65 years of age or older (mean age, 71 years; range, 65 to 82 years) were treated after cardiotomy with a centrifugal vortex or pneumatic mechanical ventricular assist device. This group comprised 1.9% of the 926 patients 65 years of age or older undergoing cardiac surgical procedures and 69% of the 26 patients requiring postcardiotomy support during this interval. Before institution of mechanical support, all patients were receiving maximal inotropic support and 16 patients had intraaortic balloon pumps inserted. Univentricular support was used in 9 patients (6 left, 3 right) and biventricular support in 9 patients. The mean duration of support was 45 hours (range, 8 to 118 hours). Twelve patients (67%) were successfully weaned, 8 (44%) were discharged from the hospital, and 6 (33%) remain alive 11 to 31 months postoperatively. Four of the 6 survivors are in New York Heart Association class I, 1 is in class II, and 1 is in class IV. The Combined Registry for ventricular assist device support has recently reported an overall survival rate of 12% in patients 65 to 70 years of age and 6% in those older than 70 years. Our results are comparable with those reported for younger patients and justify the use of postcardiotomy ventricular assist device support in the elderly.

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Several types of ventricular assist devices are currently available for temporary support of the circulation after cardiac surgical procedures. The criteria for selection of patients who are likely to derive benefit from postcardiotomy circulatory support are still evolving. This is particularly true for older patients. The largest experience with postcardiotomy mechanical circulatory support has been accumulated in younger patients [1–3]. Published reports suggest that elderly patients with postcardiotomy shock have a higher initial mortality and a lower probability of recovery than younger patients [4, 5]. We have employed mechanical circulatory support after cardiac surgical procedures in elderly patients and present the results of our experience accumulated during a recent 44-month interval.

Material and Methods

Between November 1985 and July 1989, 18 patients 65 years of age or older were supported with univentricular (9 patients) or biventricular (9 patients) mechanical circulatory devices after cardiac surgical procedures employing cardiopulmonary bypass. The mean age of the patients was 71.3 years (range, 65 to 82 years) and 61% were male. This represents 1.9% of the 926 patients 65 years of age or older who underwent cardiac surgical procedures and 69% of the 26 patients who required postoperative mechanical circulatory support during this interval. Intraaortic balloon counterpulsation was required in 93 (10%) of the patients who were 65 years of age or older.

The operative procedures performed are shown in Table 1. Sixteen of the 18 patients underwent coronary artery bypass grafting alone (10 patients) or in conjunction with other procedures (mitral valve replacement, aortic valve replacement, left ventricular aneurysmectomy, and aortic or carotid endarterectomy [6 patients]). Seven of these 16 procedures were reoperations. Two additional patients underwent emergency pulmonary embolectomy after an initially uncomplicated postoperative course following coronary artery bypass grafting 7 days previously.

Standard techniques for cannulation and cardiopulmonary bypass were employed for the cardiac surgical procedures. Intraoperative myocardial protection was achieved by infusion of 4°C oxygenated crystalloid or blood cardioplegia delivered at 250 mL/min every 20 to 30 minutes during the period of aortic occlusion. Intermittent topical cooling of the myocardium with 1 to 2 L of Ringer's solution (4°C) was also used during the period of aortic clamping. Myocardial temperature measured in the anterior ventricular septum was maintained between 10° and 15°C. The mean duration of aortic clamping was 86 ± 36 minutes (range, 18 to 145 minutes).

Previously established criteria for insertion of ventricular assist devices were used [6–8]. At least one attempt was made to wean the patients from cardiopulmonary bypass after a 30-minute interval of normothermic bypass. All patients were receiving maximal inotropic support and 16 of the 18 patients had insertion of intraaortic balloon

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Table 1. Operations Performed, Type of Support, and Results in 18 Patients 65 Years of Age and Older

Operative Procedure	No. of Patients	Type of Support: Left	Type of Support: Right	Mean Duration of Support (h)	No. Weaned	No. Discharged	No. Long-Term Survivors
Primary CABG	5	5	3	58.4	4	2	1
Reoperative CABG	5	5	2	49.5	3	2	2
CABG + MVR + LVA	2	2	2	31.5	1	1	1
Pulmonary embolectomy	2	0	2	42.0	2	2	1
CABG + AVR	1	0	1	8.0	0	0	0
CABG + aortic endarterectomy	1	1	1	22.0	0	0	0
Reoperative CABG + carotid endarterectomy	1	1	0	42.5	1	1	1
Reoperative CABG + LVA	1	1	1	77.5	1	0	0
Total	18	15	12	45.0	12 (67%)	8 (44%)	6 (33%)

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; LVA = left ventricular aneurysmectomy; MVR = mitral valve replacement.

pumps. Severe peripheral and thoracic arteriosclerosis prevented insertion of balloon pumps in the other 2 patients. The mean duration of cardiopulmonary bypass before insertion of the assist devices was 200 ± 54 minutes (range, 96 to 289 minutes). The devices were inserted at the time of operation in 16 patients and on the first and second postoperative days in the remaining 2 patients.

During the study interval, 6 patients who fulfilled the hemodynamic criteria for insertion of ventricular assist devices did not have them inserted. The decision not to employ the devices was based on the inability to satisfactorily control hemorrhage from the heart or great vessels (3 patients) or the existence of severe preoperative left ventricular dysfunction combined with presumptive evidence of extensive perioperative myocardial infarction by intraoperative echocardiography and ST-T segment changes on the electrocardiographic monitor (3 patients). None of these patients survived.

Left ventricular support was used in 6 patients, right ventricular support in 3 patients, and biventricular support in 9 patients. The Pierce-Donachy pneumatically driven pulsatile assist device (Thoratec Laboratories, Berkeley, CA) was used as a left ventricular assist device in 1 patient. Because of regulations established by the Food and Drug Administration, the Thoratec device cannot be used in patients older than 70 years. The Bio-Medicus Centrifugal Vortex Pump (Bio-Medicus, Eden Prairie, MN) was used in the remaining patients (5 left, 3 right, 9 biventricular).

The Thoratec device was inserted while the patient was on cardiopulmonary bypass. A right-angled cannula was placed into the left atrium beneath the interatrial groove and brought through the skin beneath the left costal margin. A Dacron graft attached to a second cannula was sewn onto the ascending aorta and brought through the skin of the upper abdomen through a separate incision. The cannulas were then connected to the pumping chamber and air was removed from the system. The console was set in the fill-to-empty mode with a variable rate.

The centrifugal pumps were used with several different cannulas. The aortic and two single-stage venous cannulas used for cardiopulmonary bypass were usually attached to the tubing from the centrifugal pumps. Additional cannulas were placed in the left atrium posterior to the interatrial groove for the left-sided device, and in the pulmonary artery for the right-sided device. The cannulas and tubing were tunneled subcostally and the sternal incision was closed, or the sternum was left open and the soft tissue and skin were closed around the cannulas, which exited through the incision.

During the period of support, the activated clotting time was maintained between 150 and 200 seconds by intravenous infusion of heparin. Weaning from the devices was initially attempted after 8 to 12 hours of support. Echocardiographic studies or radionuclide scans were obtained at intervals during support to assess recovery of ventricular function. With the centrifugal pump, flow was decreased to 1.0 to 1.5 $L \cdot min^{-1} \cdot m^{-2}$ and left atrial, central venous, and systemic blood pressures were measured. If the mean left atrial or right atrial pressures rose above 20 mm Hg or the systolic pressure did not rise above 90 mm Hg, flows were restored to baseline levels (2.0 to 2.5 $L \cdot min^{-1} \cdot m^{-2}$). If a favorable response was seen, the pumps were turned off transiently for measurement of cardiac output by the thermodilution technique. If the cardiac output was less than 2.0 $L \cdot min^{-1} \cdot m^{-2}$, flow was increased and further evaluation was made. If the cardiac output was 2.0 $L \cdot min^{-1} \cdot m^{-2}$ or greater, the devices were removed. With the pneumatic device, weaning was done either in the R-wave synchronized mode by decreasing the heart rate to ventricular assist device rate ratio to 1:2 or 1:3, or in the fixed rate mode by decreasing the pumping rate. Owing to the advanced age of these patients, none were considered candidates for bridging to

Table 2. Comparison of Preoperative and Intraoperative Variables Between Survivors and Nonsurvivors

Variable	Long-Term Survivors (n = 6)	Non-survivors (n = 12)	p Value
Mean preoperative LV wall motion score (CASS)	11.0	11.3	NS
PVD (%)	0	5 (61)	NS
COPD (%)	0	2 (17)	NS
Left main coronary artery disease (%)	1 (17)	4 (33)	NS
Urgent operation (%)	4 (66)	6 (50)	NS
Mean aortic clamp time ± SD (min)	93 ± 36	86 ± 36	NS
Mean duration of cardiopulmonary bypass ± SD (min)	189 ± 53	200 ± 54	NS
Units PRBC transfused (mean)	15.5	18.6	NS
Duration of support (h)	47.8	45.8	NS

CASS = coronary artery surgery study scoring system; COPD = chronic obstructive pulmonary disease; LV = left ventricle; NS = not significant ($p \geq 0.05$); PRBC = packed red blood cells; PVD = peripheral vascular disease; SD = standard deviation.

cardiac transplantation if weaning from the devices was not possible. The mean duration of support for the entire group was 45 hours and ranged from 8 to 118 hours.

Results

Mortality

Six patients (33%) could not be weaned from ventricular assist device support. Of the remaining 12 patients (67%) who were weaned from the assist devices, 4 died in the hospital (2 of ventricular arrhythmias [21 and 71 days postoperatively], 1 of congestive failure [4 days postoperatively], and 1 of respiratory arrest [63 days postoperatively]). Eight patients (44%) were discharged from the hospital and 6 of these patients (33% of the total) are alive 11 to 31 months postoperatively. The two deaths after hospital discharge occurred 60 and 74 days postoperatively and resulted from congestive heart failure and respiratory failure. At last follow-up, 4 of the 6 surviving patients are in New York Heart Association class I, 1 is in class II, and 1 is in class IV. Table 2 compares some of the preoperative and intraoperative characteristics of the 12 patients who died in the hospital and the 6 hospital survivors. Using χ^2 analysis, no statistically significant differences were observed.

Morbidity

Reoperation for bleeding was required in 6 patients (33%). Two of these patients were hospital survivors. Perioperative myocardial infarction (defined as the appearance of new Q waves on electrocardiogram in association with a serum lactic dehydrogenase$_1$/lactic dehydrogenase$_2$ isoenzyme ratio of greater than 1.0) occurred in 5 patients (28%) with 2 long-term survivors. Renal failure requiring ultrafiltration or dialysis occurred in 4 patients (22%), and 2 survived. Permanent central nervous system deficits occurred in 2 patients (11%), and neither was a long-term survivor. In 1 patient a deep sternal wound infection developed and required debridement and secondary closure; this patient survived. Prolonged ventilatory support was necessary for all 12 patients who were weaned from ventricular assist device support and averaged 22.5 days. Four of the 6 long-term survivors required tracheostomy. The mean duration of hospitalization for the 8 hospital survivors was 48 days (range, 22 to 64 days). Table 3 shows the complications that occurred postoperatively among the survivors of mechanical circulatory support. Fifty percent of the survivors had more than one major complication.

During the study interval, 838 patients younger than 65 years underwent cardiac surgical procedures. Fifty-one of these patients (6.1%) required intraaortic balloon pump support postoperatively and 8 patients (1%) were also treated with mechanical circulatory assist devices. Six of these 8 patients could not be weaned from circulatory

Table 3. Postoperative Complications in the 8 Hospital Survivors

Patient No.	Age (y)	Reoperation for Bleeding	Perioperative Myocardial Infarction	Renal Failure	Central Nervous System Deficit	Sternal Infection	Ventilatory Support >48 h
1	66	No	No	No	Yes	No	Yes
2[a]	68	No	No	No	No	No	Yes
3[a]	68	No	No	No	No	No	Yes
4[a]	70	No	No	No	No	No	Yes
5[a]	74	No	Yes	Yes	No	No	Yes
6	70	No	No	No	No	No	Yes
7[a]	72	Yes	Yes	No	No	Yes	Yes
8[a]	67	Yes	No	Yes	No	No	Yes

[a] Long-term survivor.

Table 4. Postoperative Complications According to Age in Patients Requiring Postcardiotomy Mechanical Circulatory Support

Complication	<65 Years (n = 8)	≥65 Years (n = 18)	*p* Value
Reoperation for bleeding	1 (12%)	6 (33%)	NS
Perioperative myocardial infarction	4 (50%)	5 (28%)	NS
Renal failure	1 (12%)	4 (22%)	NS
Central nervous system deficit	2 (25%)	2 (11%)	NS
Sternal infection	1 (12%)	1 (6%)	NS

NS = not significant ($p \geq 0.05$).

support. Two of the 6 were successfully bridged to heart transplantation and are long-term survivors (40 and 44 months postoperatively). One patient was weaned but died on the 24th postoperative day. The remaining patient from this group (12.5% of the total) was successfully weaned and is alive 16 months postoperatively. Renal failure occurred in 1 patient who did not survive. New central nervous system deficits occurred in 2 patients with 1 survivor. One patient required reoperation for bleeding and one had a sternal wound infection; neither survived. Respiratory insufficiency requiring tracheostomy developed in 5 patients (62.5%) in this group. A comparison of the complication rates for the younger and older patients is shown in Table 4. None of the differences were statistically significant.

Comment

Impaired cardiac performance immediately after cardiac surgical procedures is a significant predictor of early death. The hemodynamic criteria for the presence of severe ventricular dysfunction in this setting have been established and include a mean left or right atrial pressure of greater than 20 mm Hg, a systolic blood pressure less than 90 mm Hg, and a cardiac index of less than 2.0 $L \cdot min^{-1} \cdot m^{-2}$ [6–8]. In addition to these hemodynamic variables, intraoperative echocardiography may be useful in defining the need for mechanical circulatory support. Transesophageal Doppler color flow echocardiography can demonstrate regional and global wall motion abnormalities as well as valvular insufficiency and the presence of intracardiac shunts. Changes in contractility resulting from inotropic therapy and intraaortic balloon pump support can also be determined [9–11]. The decision to insert a ventricular assist device is made when inotropic support and balloon counterpulsation are ineffective in maintaining adequate cardiac function. This decision, particularly in older patients, requires a thorough understanding of the probability of a successful outcome, the frequency and severity of postoperative complications, and the costs of such interventions.

Several investigators have recently reported long-term survival rates of 22% to 50% with good to excellent functional status in younger patients (mean age range, 52 to 57 years) treated with ventricular assist devices postoperatively [11–13]. The results with older patients are less certain. The Combined Registry for the clinical use of mechanical ventricular assist devices of The American Society for Artificial Internal Organs and The International Society for Heart Transplantation has recently reported a hospital discharge rate of 19.3% for patients 60 to 69 years of age and 10.2% in patients older than 70 years [14]. This group has previously reported a long-term survival of 12% among patients 65 to 70 years of age and only 6% among patients older than 70 years [4]. These results have tempered the enthusiasm of many surgeons for inserting ventricular assist devices in elderly patients.

Our review indicates that postcardiotomy support was required twice as often in the elderly group as in the younger patients. With the continued aging of the population of patients who undergo cardiac operations and an increase in the number who require urgent or emergent operation, the percentage of patients in whom severe left ventricular dysfunction develops postoperatively and who could benefit from mechanical circulatory support may actually increase. Furthermore, this elderly group has a high incidence of diabetes mellitus, peripheral vascular disease, and female patients. These are risk factors that increase the frequency of vascular complications after insertion of intraaortic balloon pumps and may even preclude their use [15, 16]. Severe aortic and peripheral atherosclerosis prevented the insertion of balloon pumps in 2 of the patients in our series. Inability to institute balloon support or the probability of a serious vascular complication after insertion may become more prevalent indications for insertion of a ventricular assist device, particularly in elderly patients. Although optimal methods of intraoperative myocardial protection will minimize the need for mechanical support, it seems unlikely that the need for such support will ever be totally eliminated.

The concept of reversible postischemic myocardial stunning with eventual recovery rather than permanent ventricular dysfunction proposed by Braunwald and Kloner [17] has led to the hypothesis that some patients who sustain potentially reversible myocardial injury during cardiac surgical procedures will recover clinically significant myocardial function if the workload on the myocardium can be substantially reduced. A perioperative myocardial infarction, on the other hand, has been shown to have an adverse effect on survival in postcardiotomy patients supported with ventricular assist devices [18]. However, differentiation between stunned and infarcted myocardium in the immediate postoperative period can be difficult. The severity of preoperative ventricular dysfunction may not be a useful predictor unless the dysfunction is severe [18]. In our series, there was no significant difference in the severity of preoperative left ventricular dysfunction as assessed by left ventricular wall motion score between the survivors and nonsurvivors (see Table 2).

Selection of the appropriate ventricular assist device for a particular patient is based on several factors. In general, myocardial stunning alone allows an early return of ventricular function. In our study, the mean duration of mechanical circulatory support was 45 hours. Other authors have reported mean durations from 35 to 94 hours [1, 3, 5, 19]. The centrifugal vortex pump has been used for up to 30 days [20]. However, after 7 to 10 days a significant increase in complications has been observed [2, 9]. This device is readily available, is relatively inexpensive, and can be used with a variety of cannulas and in patients of any age. The Pierce-Donachy (Thoratec) pneumatic ventricular assist device has been used in 102 patients after cardiotomy with 18 survivors and an average duration of support of 3.5 days [21]. However, the restrictions currently imposed by the Food and Drug Administration for insertion of this device and its substantial cost limit its use in older patients. No clear advantage of pneumatically driven devices over centrifugal pumps for short-term, postcardiotomy support has been demonstrated. The Combined Registry reports a discharge rate of 56.9% in 121 patients treated with pneumatic devices and 51.5% in 283 patients supported by centrifugal pumps [14]. We therefore believe that the centrifugal vortex pump is the most appropriate device for postcardiotomy mechanical support in older patients.

The results of our study suggest that implementation of temporary mechanical ventricular assistance for treatment of postcardiotomy shock should not be restricted to younger patients. Our results in patients 65 years of age and older did not differ appreciably from those reported for younger patients. Although this intervention can be costly, the excessive mortality without mechanical circulatory support for patients who cannot be weaned from cardiopulmonary bypass and the excellent long-term functional status of the majority of survivors justify its continued use in older patients.

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Risk Factors for Cardiac Operations in Adult Jehovah's Witnesses

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During a 27-year-period, 663 adults of the Jehovah's Witness faith underwent open heart procedures at the Texas Heart Institute. To determine the effect of recent changes in operative techniques and in the patient population itself on early mortality, we reevaluated the surgical outcome in this special group of patients. We reviewed the charts of 88 consecutive Jehovah's Witness patients who had an open heart operation between January 1986 and March 1989 and compared demographic variables in this group with those of 575 patients who underwent operation between May 1963 and January 1986. In our recent series, patients were older (mean age, 61 years versus 54 years), and 16% were seen for repeat procedures. Early mortality (≤30 days postoperatively) was lower in the recent series than in the earlier series (7.0% versus 10.7%), but the difference between the groups was not statistically significant. We identified several important factors associated with an increased risk of early death in the recent group of patients. These factors included repeat cardiac operations ($p < 0.01$), especially for valvar dysfunction, severe left ventricular dysfunction (defined as an ejection fraction < 0.35) ($p < 0.01$), and a hemoglobin level lower than 80 g/L (8 g/dL) ($p < 0.01$) on postoperative day 1. Although blood loss remains the leading cause of death in these patients, cardiac operations can be performed with an acceptable mortality.

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More than 663 patients of the Jehovah's Witness faith have undergone open heart procedures with the use of cardiopulmonary bypass at the Texas Heart Institute during its 27-year history. Surgical intervention in this particular patient population is complicated by their church law, which forbids use of blood transfusions or any blood derivatives. However, the development of the bloodless prime technique of extracorporeal circulation in the early 1960s made cardiac operations possible in these patients [1–4].

Our experience [5–9] with cardiac and noncardiac vascular procedures in patients who are Jehovah's Witnesses has been reported previously. Recently, the adult patient population seen for cardiac operations has changed, and the operative techniques have also been modified. Today, more patients are seen for reoperation, and the internal mammary artery is increasingly being used as a conduit in coronary artery revascularization. We recently evaluated our surgical experience in adult Jehovah's Witness patients to determine changes in demographics and factors that influenced mortality. These factors should serve as important predictors of surgical feasibility in this special group of patients.

Material and Methods

Patient Population

Using our computer database, we undertook a retrospective review of 88 consecutive adult Jehovah's Witness patients (>18 years of age) who underwent open heart procedures between January 1986 and March 1989. Possible risk factors were identified in this group and analyzed by using the Mantel-Haenszel χ^2 formula. A comparison of demographic variables was made between these patients and an earlier series of patients seen from May 1963 to January 1986.

There were 33 women (37.5%) and 55 men (62.5%) in the recent group; the average age was 61 years. In this group of patients, we examined the following factors to determine their association with increased operative risk: age, sex, type of operation performed, ejection fraction, hemoglobin level (preoperative, immediately postoperative, postoperative day 1, and discharge), and major complications, including the need for reoperation to control bleeding.

Between May 1963 and January 1986, 575 adults of the Jehovah's Witness faith underwent open heart procedures. In this group, we reviewed factors such as age, sex, type of operation performed, and early mortality (<30 days).

Technical Considerations

Patients usually underwent procedures when the preoperative hemoglobin level was 120 g/L or greater (≥12 g/dL). When appropriate, ferrous sulfate (Feosol) was given preoperatively to stimulate erythropoiesis and raise the hemoglobin to desired levels.

During operation, meticulous attention was given to hemostasis and application of efficient surgical techniques. Temporary cardiopulmonary bypass under normothermic or mildly hypothermic conditions was used. Bubble oxygenators were primed with 20 to 40 mL/kg

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Table 1. Open Heart Procedures, May 1963 to March 1989

Procedure	No. of Patients
Aortocoronary bypass	308
Aortic valve replacement[a]	155
Mitral valve repair or replacement	155
Atrial septal defect repair	16
Left ventricular aneurysm repair	3
Orthotopic cardiac transplantation	5
Miscellaneous procedures	21
Total	663

[a] Three of these patients had concomitant repair of an ascending aortic aneurysm using a composite fabric graft containing a synthetic valve.

body weight and flow rates averaged 40 to 100 mL/kg. After weaning from cardiopulmonary bypass, all blood from the heart-lung machine was returned to the patient. Postoperatively, all shed mediastinal blood was collected in the cardiotomy reservoir and intravenously returned to the patient. For the last 12 months, we have routinely used a Haemonetics Cell Saver—before heparin sodium is given and after protamine sulfate is given—to salvage blood that would otherwise be discarded. One unit of blood is usually recovered in this way.

At no time was blood or blood products given to these patients, and volume was replaced with crystalloid solutions. Dextran and hetastarch were avoided because of their known adverse effects on coagulation in hemodiluted patients.

Results

Types of open heart procedures in the total population of adult Jehovah's Witnesses from May 1963 to March 1989 are listed in Table 1. The overall early mortality rate (≤ 30 day) in this group was 10.7% [5]. In our most recent group of 88 patients (Table 2), early mortality was slightly lower. Of these 88 patients, 74 (84%) underwent primary procedures; the mortality rate was 2.7%. The other 14 underwent repeat operation; 4 died (28.6%) ($p < 0.01$). Female sex was associated with an increased mortality rate (9.1% versus 5.5%), but the difference was not significant ($p = 0.51$).

The average preoperative hemoglobin level was 137 g/L (13.7 g/dL) in survivors versus 130 g/L (13 g/dL) in nonsurvivors. Immediately after operation, the average hemoglobin level was 87 g/L (8.7 g/dL) in survivors and 81 g/L (8.1 g/dL) in nonsurvivors. Although there was no significant increase in risk associated with a low hemoglobin level (<80 g/L [<8.0 g/dL]), no patient who had a hemoglobin level of 100 g/L or higher ($\geq$10.0 g/dL) immediately after operation died. On postoperative day 1, however, a hemoglobin level lower than 80 g/L (<8 g/dL) was strongly associated with an increased risk of early death ($p = 0.001$). On postoperative day 1, the average level was 97 g/L (9.7 g/dL) in survivors and 65 g/L (6.5 g/dL) in nonsurvivors. This factor became even more significant at the time of death or hospital discharge; the average hemoglobin level was 95 g/L (9.5 g/dL) in survivors and 56 g/L (5.6 g/dL) in nonsurvivors ($p < 0.01$).

Two patients were returned to the operating room in the immediate postoperative period because of hemorrhage; 1 of them died of blood loss. The overall early mortality rate was 7% (6 patients). Blood loss was the cause of death in 3 patients; the average hemoglobin level at the time of death was 40 g/L (4 g/dL). In the other 3 patients, blood loss was a major contributor to death; the average hemoglobin level at the time of death was 72 g/L (7.2 g/dL).

The preoperative ejection fraction (based on cineangiography) averaged 0.49 in the patients who survived operation and 0.37 in the 6 patients who died. In the patients undergoing repeat double-valve procedures, the average ejection fraction was 0.30. An ejection fraction of

Table 2. Open Heart Procedures, January 1986 to March 1989[a,b]

Procedure	Primary Operations/Deaths	Reoperations/Deaths	Total Operations/Deaths	Mortality (%)
Isolated ACB				
With IMA	31/2	6/1	37/3	8
Without IMA	21/0	1/0	22/0	0
Isolated AVR	5/0	1/0	6/0	0
Isolated MVR or repair	7/0	1/0	8/0	0
Multiple-valve replacement	2/0	5/3	7/3	43
ACB + valve procedure (any type)	5/0	. . .	5/0	0
ASD repair	3/0	. . .	3/0	0
Total	74/2 (2.7)	14/4 (29)	88/6 (7)	. . .

[a] The overall mortality was 11.5% for valve procedures (with or without ACB) and 5% for isolated ACB. The mortality was 14% among patients undergoing isolated ACB as a reoperation versus 4% among those undergoing ACB for the first time. [b] Numbers in parentheses are percentages.

ACB = aortocoronary bypass; ASD = atrial septal defect; AVR = aortic valve replacement; IMA = internal mammary artery; MVR = mitral valve replacement.

less than 0.35 was associated with a significantly increased risk of early death ($p < 0.01$).

Most of the 88 patients (59 patients or 67%) underwent isolated coronary artery revascularization, and the internal mammary artery was used in 63%. Use of this artery, however, was not a significant risk factor for early death ($p = 0.81$). Multiple-valve replacement was performed in 7 patients. Three of the 5 having a repeat procedure died.

Six (7.3%) of the 82 survivors had wound complications. Sternal revision was required in 4 patients, and in 1 patient, an omental pedicled flap covered by a split-thickness skin graft was required because of sternal osteomyelitis. Two of the 6 patients who died had major wound complications necessitating sternal revision, and in each, death occurred early after the second operation. Postoperative renal dysfunction developed in 2 (2.4%) of the 82 survivors, but neither required dialysis. Two of the 6 patients who died early had undergone dialysis for renal failure. One of the 82 survivors sustained a sudden cardiac arrest in the early postoperative period, and 1 had a perioperative myocardial infarction.

Comment

That cardiac operations can be performed in Jehovah's Witness patients has been clearly documented previously [5–10] even in very young children. In 1985, our group [11] reported its surgical experience with 73 children of Jehovah's Witnesses; all the children were less than 2 years of age. Fifteen had open intracardiac repair of congenital anomalies with use of cardiopulmonary bypass. There were no deaths in that series. Recently, however, the patient population has changed. Increasing numbers of patients of the Jehovah's Witness faith are being seen for repeat procedures after previous valve procedures or coronary artery revascularization. Many of them have severe left ventricular dysfunction. The internal mammary artery has been increasingly used as a conduit in the aortocoronary bypass operation, and even with the greater complexity of operations, mortality has not increased. In the 88 patients from our most recent series, no deaths occurred in patients with ejection fractions greater than 0.35 and hemoglobin levels of 100 g/L or greater (≥ 10 g/dL) in the immediate postoperative period.

Several improved techniques in operative management have helped us to maintain a low mortality, including improved myocardial protection with crystalloid cardioplegia and postoperatively salvaging blood with the cardiotomy reservoir. Recently, we have achieved impressive results using the Haemonetics Cell Saver intraoperatively. Commonly, 1 to 2 units of blood that would otherwise be lost is salvaged with this device. Since the introduction of this technique, no patient has died secondary to blood loss or anemia. Previous cardiac operations—especially prior valve procedures—represent a strong risk factor for early death. In our series, there was a 29% mortality among the 14 patients who underwent reoperation versus a 2.7% mortality for patients undergoing initial cardiac operations. Nevertheless, blood loss and anemia remain the primary factors associated with early mortality. As a result of all the recent improvements in operative technique, however, the operative mortality in Jehovah's Witness patients has decreased, even though the patient population is older and sicker. Keeping risk factors in mind, we believe that patients of the Jehovah's Witness faith can undergo operation successfully and return to productive lives.

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Hemodynamic Effects of Lobar Pulmonary Artery Occlusion in a Porcine Sepsis Model

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We induced severe pulmonary hypertension and acute lung injury in 6 pigs by *Pseudomonas aeruginosa* infusion. We studied the effect of pulmonary artery catheter balloon inflation on hemodynamics. After bacterial infusion, inflation of a pulmonary artery catheter balloon in the left lower lobar pulmonary artery was accompanied by a significant ($p < 0.05$, paired t test) increase in pulmonary artery pressure, a decrease in left atrial pressure, a decrease in cardiac output, and a decrease in mean arterial pressure. No significant changes occurred when the catheter was advanced into the wedged position without balloon inflation. Balloon inflation had no significant effect on these variables before bacterial infusion. We conclude that with sufficiently severe pulmonary hypertension in association with diffuse lung injury, lobar pulmonary artery occlusion may cause alterations in cardiac output and left atrial pressure. This may confuse interpretation of pulmonary artery catheter measurements.

(Ann Thorac Surg 1991;51:451–4)

Recently Willis and associates [1] reported a patient with pulmonary edema after right pneumonectomy in whom systemic hypotension was induced each time the balloon of a balloon-tipped pulmonary artery catheter was inflated. The chest radiograph showed the tip of the pulmonary artery catheter to be in the left lower lobar pulmonary artery where balloon inflation would force the entire cardiac output (CO) to flow through the left upper lobe. They suggested that systemic hypotension was related to a reduction in CO caused by an acute increase in right ventricular afterload and a resultant reduction in left ventricular filling.

In dogs with normal lungs, Wittnick and co-workers [2] measured the pulmonary artery occlusion pressure (PAOP) by balloon inflation and by catheter advancement without balloon inflation before and after pneumonectomy. Before pneumonectomy the PAOP measured by the two techniques was equal and neither was associated with a decrease in left atrial pressure (LAP). After pneumonectomy, balloon inflation, but not catheter advancement, caused a reduction in LAP and mean systemic arterial pressure (AP).

Pulmonary arterial hypertension may complicate late-stage adult respiratory distress syndrome in humans in association with obliterative pulmonary vascular changes [3]. Provided restriction of the pulmonary vascular bed were of sufficient severity, similar hemodynamic changes would be expected to occur in this setting. In pigs, *Pseudomonas aeruginosa* infusion results in widespread pulmonary vascular occlusion, severe pulmonary hypertension, and diffuse lung injury [4] mimicking this situation. We therefore examined the effects of pulmonary artery catheter balloon inflation in this model to determine what hemodynamic changes occur without surgical resection of lung tissue and whether the mechanism of these changes is further reduction of the pulmonary vascular bed as in animals having undergone pneumonectomy.

Material and Methods

Studies were performed on 6 pigs (10 to 13 kg) that were supine, intubated, and anesthetized with pentobarbital (25 mg/kg initially, supplemented by additional intravenous doses as required). All animals were mechanically ventilated using a volume-cycled ventilator with a tidal volume of 15 mL/kg, a respiratory rate of 14 breaths/min, and an inspired oxygen concentration of 1.00. Through the right femoral vein a pulmonary artery catheter (Edwards 93A-118-7F) was positioned, using fluoroscopy, in the right lower lobe. A left thoracotomy was then done. Using the left femoral vein, a second identical catheter was positioned by direct palpation in the left lower lobe pulmonary artery.

The catheter in the left lower lobe was used to measure the PAOP. Mean pulmonary artery pressure (PAP) and thermodilution CO were measured using the catheter in the right lower lobar pulmonary artery. Left atrial pressure was measured using a catheter placed in the left atrium through the atrial appendage at the time of thoracotomy. Mean systemic arterial pressure was recorded from a catheter in the left femoral artery. Chest tube drainage was used to evacuate residual air from the left hemithorax after closure of the thoracotomy incision. One liter of 0.9% saline solution was given intravenously during the surgical procedures. All vascular pressures were measured using Statham 23ID transducers and recorded on an 8-channel strip chart recorder (HP 7758B).

Baseline measurements of AP, PAP, LAP, and CO were obtained before and during inflation of the left lower lobar

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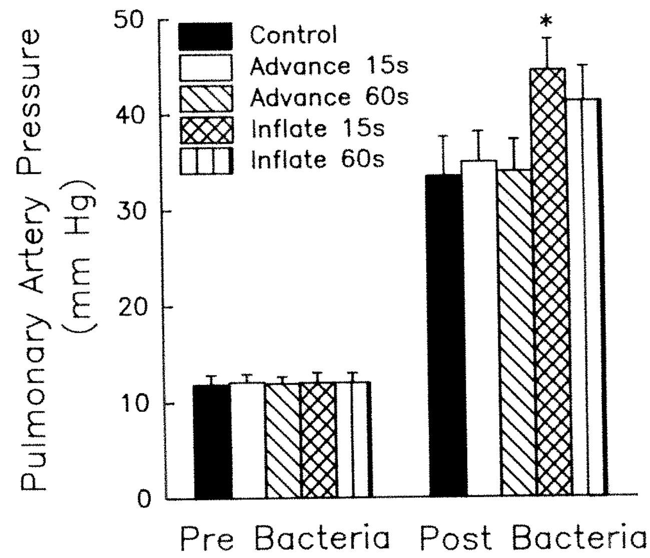

*Fig 1. Pulmonary artery pressure before (*Pre Bacteria*) and after (*Post Bacteria*) infusion of* Pseudomonas aeruginosa *suspension.* Control *refers to the absence of pulmonary artery occlusion.* Advance *indicates pulmonary artery occlusion by advancement of the left pulmonary artery catheter into the wedged position.* Inflate *indicates pulmonary artery occlusion by inflation of the balloon of the left pulmonary artery catheter. Data at 15 and 60 seconds after pulmonary artery occlusion are illustrated. (*$p < 0.05$ for the difference between the marked condition and the corresponding control.)*

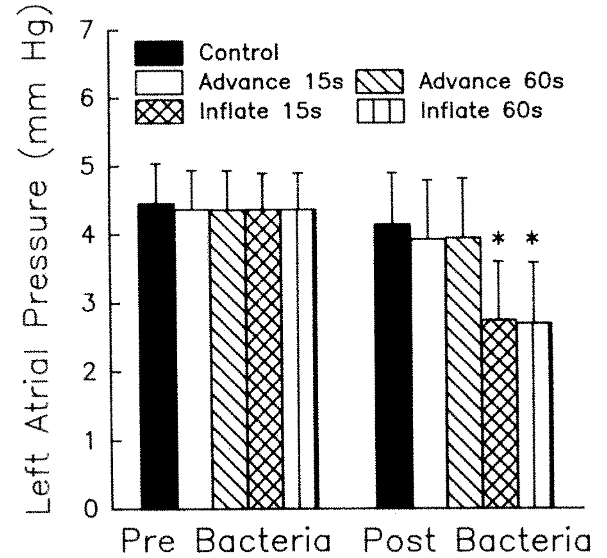

*Fig 2. Left atrial pressure recorded before (*Pre Bacteria*) and after (*Post Bacteria*) infusion of* Pseudomonas aeruginosa *suspension.* Control, Advance, *and* Inflate *conditions at 15 and 60 seconds after pulmonary artery occlusion are as described in Figure 1. (*$p < 0.05$ for the difference between the marked condition and the corresponding control.)*

pulmonary artery catheter balloon. The balloon was then deflated, the catheter was advanced into the wedged position without balloon inflation, and the measurements were repeated. Achievement of the wedged position was determined by the loss of the normal systolic pulse wave in the PAP tracing and a recorded pressure equal to or lower than the pulmonary arterial diastolic pressure [5, 6]. One hundred milliliters of a suspension of *Pseudomonas aeruginosa* (10^8 colony forming units/mL) in 0.9% saline solution was then infused intravenously over 1 hour. Thirty minutes after the bacterial infusion was complete, the hemodynamic measurements before and during left lower lobe pulmonary artery balloon inflation and before and during catheter advancement were repeated. The CO during pulmonary artery occlusion was taken as the average of three determinations performed in rapid succession after the onset of occlusion. The values for LAP, AP, PAP, and PAOP were taken as those recorded at 15 and 60 seconds after occlusion. Differences between conditions were compared using paired two-tailed t tests and judged to be significant if p was less than 0.05.

Results

Figures 1, 2, and 3 illustrate the changes in PAP, LAP, and CO, respectively, under each of the experimental conditions. Before administration of the bacterial suspension, no significant change in any hemodynamic variable accompanied occlusion by either technique. The hemodynamic variables 30 minutes after infusion of the bacterial suspension without pulmonary artery occlusion, compared with preinfusion control conditions, changed as follows (mean ± standard error): PAP increased from 11.8 ± 1.1 to 33.5 ± 4.0 mm Hg, CO decreased from 3.00 ± 0.31 to 2.41 ± 0.35 L/min, AP decreased from 94.2 ± 3.4 to 66.2 ± 5.2 mm Hg, and LAP did not change significantly (4.5 ± 0.6 versus 4.2 ± 1.1 mm Hg).

Inflation of the left lower lobar pulmonary artery catheter balloon after bacteria administration resulted in a

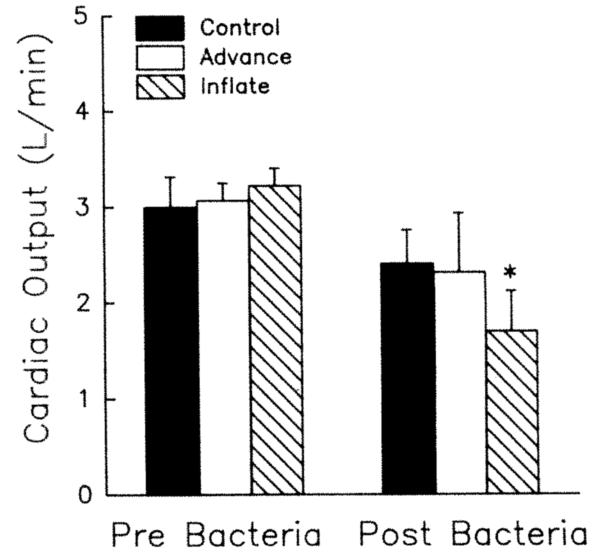

*Fig 3. Cardiac output recorded before (*Pre Bacteria*) and after (*Post Bacteria*) infusion of* Pseudomonas aeruginosa *suspension.* Control, Advance, *and* Inflate *conditions are as described in Figure 1. (*$p < 0.05$ for the difference between the marked condition and the corresponding control.)*

decrease in arterial pressure from the control value of 66.2 ± 5.2 to 58.5 ± 5.1 mm Hg ($p < 0.05$). This was accompanied by a further significant increase in PAP, a decrease in LAP, and a decrease in CO. There was no significant change in these variables between 15 and 60 seconds of occlusion, suggesting stability of the animals' hemodynamics over the time required for the CO measurements.

Advancing the catheter into the wedge position was associated with much smaller changes in LAP, PAP, CO, and AP, none of which were statistically significant.

After bacterial infusion the PAOP recorded during balloon inflation was less than that recorded by advancing the catheter (3.13 ± 0.65 versus 4.47 ± 0.73 mm Hg; $p < 0.05$).

Comment

We have found that lobar pulmonary artery occlusion in the setting of severe pulmonary hypertension and diffuse lung injury was accompanied by a decrease in CO (mean change = 29.4%), a decrease in LAP, and an increase in PAP. The PAOP measured by balloon inflation was less than that measured by catheter advancement. These findings are similar to those reported to occur after pneumonectomy [2].

Willis and associates [1] hypothesized that these changes may be related to reduction of the pulmonary vascular cross-sectional area resulting in increased right ventricular afterload and reduction in CO. In addition, because the rate of filling of the left atrium and left ventricle would be acutely reduced, the left ventricular and left atrial end-diastolic pressure would also decrease. This reduced pressure would be accurately measured by the balloon-tipped pulmonary artery catheter. This was supported by the findings of Wittnick and co-workers [2] in dogs with normal lungs after pneumonectomy.

In any individual situation the interactions responsible for the hemodynamic response to an increase in resistance to pulmonary blood flow may be more complex than can be characterized by simple measurements of the pressure changes. The increase in PAP may have altered the diastolic compliance of the left ventricle through its mechanical interaction with the right ventricle [7], and the reduction in CO itself may have modified further increments in PAP. The adequacy of the remaining pulmonary capillary bed, the contractility of the right ventricle (which will determine its ability to compensate for the increased afterload), and the contractility of the left ventricle (determining its ability to maintain stroke volume in the face of a reduced end-diastolic volume) are all likely to play an important role.

In the present study, the model chosen was one of acute lung injury with low left atrial and left ventricular end-diastolic pressures. The left atrium and ventricle would be on the high compliance region of their pressure-volume relationships. Under these conditions a large reduction in the filling of the left heart on balloon inflation may result in only a modest decrease in left atrial pressure. If the experimental model chosen had been that of high-pressure pulmonary edema the left heart would be on the less compliant limb of its pressure-volume relationship. One might then expect balloon inflation to result in a much larger decrease in left atrial and left ventricular end-diastolic pressures.

Although the hemodynamic effects of balloon inflation may be avoided by measuring the PAOP after catheter advancement, wedging the catheter in a smaller pulmonary artery segment will record the pressure further upstream in the pulmonary veins than will occlusion of a larger vessel [8]. The difference in the PAOP measured by the two techniques, therefore, reflects not only the induced difference in LAP but also the flow resistive pressure loss between the two points at which pressure is being recorded. Furthermore, this technique cannot be recommended for clinical use because of the potentially fatal complication of pulmonary artery rupture [9].

Despite problems in relating the PAOP to LAP under some conditions [10–12], the assessment of PAOP using the pulmonary artery catheter is one of the most important procedures currently in use for guiding fluid therapy [13]. Our results indicate another possible factor complicating the interpretation of such recordings. In the setting of diffuse lung disease with pulmonary hypertension the PAOP obtained by balloon inflation, although accurately reflecting the LAP, may not be representative of conditions that prevail when the balloon is not inflated. This would result in underestimation of the true left ventricular filling pressure and may lead to inappropriate fluid administration. The finding of a decrease in arterial pressure with balloon inflation should alert the clinician to the possibility of balloon-induced hemodynamic changes and the need to take these into account when interpreting the results of PAOP measurements. This study has not excluded the possibility of the occurrence of a falsely lowered LAP in the absence of systemic hypotension.

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The European Association for Cardio-Thoracic Surgery

Notice of Annual Meeting

The Fifth Annual Meeting of the European Association for Cardio-Thoracic Surgery will be held September 22–25, 1991, at the Royal Lancaster Hotel in London, United Kingdom. The scientific sessions are open to all registered participants. The registration fee includes admission to the entire scientific program, meeting documentation, welcome reception on Sunday evening, concert on Monday evening, and tea and coffee.

Registration and Hotel Reservation

All participants of the meeting should request a registration form from Conference Associates & Services Ltd, EACTS, Congress House, 55 New Cavendish St, London W1M 7RE, United Kingdom (telephone: 071 486 0531; facsimile: 071 935 7559).

Reoperation for Persistent Outflow Obstruction in Hypertrophic Cardiomyopathy

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This study compares results of a second left ventricular myotomy and myectomy (M+M) with those of mitral valve replacement (MVR) as reoperative procedures for persistent left ventricular outflow obstruction after M+M in hypertrophic cardiomyopathy. Comparison of the second M+M group (n = 12) with the MVR group (n = 11) disclosed significant differences ($p < 0.05$) in mean age at the initial operation (29 ± 11 years versus 40 ± 8 years), interval between operations (46 ± 57 months versus 18 ± 13 months), and age at reoperation (33 ± 10 years versus 42 ± 8 years); and insignificant differences in mean preoperative functional class, cardiac index, left ventricular outflow gradients at rest or with provocation, and hospital mortality at reoperation (2/12 versus 1/11). At 6 months after reoperation, comparison of results of a second M+M with MVR showed that mean functional class, cardiac index, and left ventricular outflow gradient at rest were similarly improved, but the outflow gradient with provocation was significantly higher in the second M+M group (57 ± 44 mm Hg versus 14 ± 9 mm Hg, $p < 0.05$). Total follow-up was 108 patient-years (100% complete) with an average of 5.9 years per patient in the second M+M group and 3.4 years per patient in the MVR group. Actuarial survival, including hospital mortality, at 3 and 5 years was 83% and 76%, respectively, after the second M+M, which was similar to 92% and 77% after MVR. Thus, either a second M+M or MVR is effective in relieving the hemodynamic obstruction and decreasing symptoms, but a second M-M is preferable because complications of anticoagulation and substitute valves are avoided.

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Operative treatment of hypertrophic cardiomyopathy was initiated in 1958 by Cleland and associates [1, 2], who performed transaortic left ventricular myotomy. Numerous authors since then have reported results of various operations to relieve left ventricular outflow obstruction in hypertrophic cardiomyopathy [3, 4]. At the National Heart, Lung, and Blood Institute, 535 patients have undergone 551 operations for hypertrophic cardiomyopathy from 1959 to 1990. Reoperation for persistent left ventricular outflow obstruction was performed in 23 patients, 12 of whom had a second left ventricular myotomy and myectomy (M+M) and 11 of whom had mitral valve replacement (MVR). This report compares results of these two procedures at reoperation.

Material and Methods

The clinical records of the Surgery Branch, National Heart, Lung, and Blood Institute were searched by computer to identify all patients who underwent reoperation for hypertrophic cardiomyopathy. Twenty-seven patients were identified and their records were reviewed.

Three of the 27 patients underwent reoperation for pure mitral regurgitation without associated left ventricular outflow obstruction, and they were excluded from further analysis as was 1 patient who underwent combined coronary artery bypass and a second M+M. The indication for reoperation in the remaining 23 patients was persistent left ventricular outflow obstruction with or without mitral regurgitation. Myotomy and myectomy was the initial operation in all 23 patients. The initial operation was performed at the National Institutes of Health in 16 of the 23 patients and at other medical centers in 7 patients.

The reoperative procedures were all performed at the National Institutes of Health. Twelve of the 23 patients underwent a second M+M and the other 11 patients underwent MVR. A second M+M was performed in all 7 patients in whom the initial M+M was performed at a different institution. Likewise, all patients who underwent MVR at reoperation had undergone the previous M+M at the National Institutes of Health. The operative techniques used in M+M were described by Morrow [3] in 1978, and those used in MVR were described by McIntosh and associates [5] in 1988. The excised mitral valves from the 11 patients who underwent MVR were reexamined.

Follow-up after reoperation was routinely achieved by yearly outpatient clinic visits, the findings from which were reviewed. The patients were also contacted by telephone after January 1, 1990, to update their records. The study period extended from 1959 to 1990. Total postoperative follow-up was 108 patient-years (100% of potential follow-up) with a mean of 5.9 years per patient

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in the second M+M group and 3.4 years per patient in the MVR group. Preoperative and postoperative data within each group were compared using paired Student's t tests. Data between each group were compared using unpaired Student's t tests and the Mantel-Haenszel test. Average values in each group are expressed as a mean ± standard error of the mean.

Results

Repeat Myotomy and Myectomy

Clinical observations on the 12 patients are presented individually in Table 1. The ages of the patients at the initial operation ranged from 8 to 45 years (mean, 29 years); 7 were men and 5 were women. Left ventricular outflow obstruction of varying degrees was the indication for the initial operation in all patients. Only 1 patient (Table 1, patient 2) had severe mitral regurgitation in addition to left ventricular outflow obstruction. Four of the 12 patients had reports of preoperative echocardiograms, which indicated in each a maximal ventricular septal thickness greater than 18 mm and systolic anterior motion of the anterior leaflet of the mitral valve. The amount of ventricular septum resected was unknown in 7 patients, 6 of whom had M+M at a medical center other than the National Institutes of Health.

The interval from initial M+M to a second M+M ranged from 6 days to 168 months (mean, 46 months). Cardiac catheterization was performed during the interval in the 12 patients, and persistent left ventricular outflow obstruction was evident in each patient. Two patients (Table 1, patients 6 and 12) also had severe mitral regurgitation. The ages of the patients at reoperation ranged from 22 to 48 years (mean, 33 years). Fatal hemorrhage occurred during reoperation from laceration of the posterior wall of the ascending aorta before the planned M+M in 2 of the 12 patients (Table 1, patients 2 [1976] and 9 [1977]). The amount of ventricular septum resected in the other 10 patients ranged from 0.6 to 3.5 g (mean, 1.9 g). These 11 patients survived a second M+M and were discharged from the Clinical Center.

At 6 to 12 months after reoperation, 7 patients were symptomatically improved, 2 were unchanged, and 1 was symptomatically worse. Mean functional class in the 10 hospital survivors was significantly improved from that preoperatively (2.0 versus 3.0, $p < 0.05$). Cardiac catheterization was performed in 9 of the 10 patients, and the left ventricular outflow gradient in each was either decreased or absent. The mean outflow gradient at rest and with provocation (use of isoproterenol or other maneuver noted in Table 1) postoperatively was significantly lower than that preoperatively although mean cardiac indices were unchanged. Four of the 11 patients had significant obstruction (> 50 mm Hg) during provocation with intravenous isoproterenol or Valsalva maneuver. The mitral regurgitation was mild postoperatively in the 2 patients in whom it was previously severe. Two of the 10 hospital survivors subsequently underwent MVR for persistent left ventricular outflow obstruction (Table 1, patients 1 and 10). Both patients survived this third operation, but 1 (Table 1, patient 1) died 18 months later of congestive heart failure, 52 months (4.3 years) after the second M+M. Only 1 other patient (Table 1, patient 11) died during the follow-up period, and the cause was a ventricular arrhythmia. An actuarial survival curve of the 12 patients who underwent a second M+M is presented in Figure 1. The acturial survival at 3 and 5 years was 83% and 76%, respectively, including the two operative deaths.

Mitral Valve Replacement

Clinical observations on each of the 11 patients who underwent MVR after M+M are presented in Table 2. The ages of the patients at the initial operation ranged from 29 to 58 years (mean, 40 years); 5 were men and 6 were women. Left ventricular outflow obstruction was the indication for initial M+M in all patients. One patient (Table 2, patient 8) also had severe mitral regurgitation. All patients underwent preoperative echocardiography, which disclosed in each a maximal ventricular septal thickness of 18 mm or more and a systolic anterior motion of the anterior mitral leaflet. Myotomy and myectomy had been performed at the National Institutes of Health in all patients, and the amount of ventricular septum resected ranged from 0.9 to 6.0 g (mean, 2.4 g).

The interval between M+M and MVR ranged from 1 day to 47 months (mean, 18 months). In 2 patients (Table 2, patients 8 and 9), MVR was performed within 7 days of the M+M. Cardiac catheterization was performed during the interval in all 11 patients, each of whom had persistent left ventricular outflow obstruction. None had severe mitral regurgitation. The ages of the patients at reoperation ranged from 30 to 60 years (mean, 42 years). A Björk-Shiley prosthesis was inserted in 8 patients, and a St. Jude Medical prosthesis in 3 patients. Each of the excised mitral valves was focally but extensively thickened by fibrous tissue without calcific deposits. Each valve was typical of that observed in patients with hypertrophic cardiomyopathy [6]. All 11 patients survived reoperation, but 1 patient (Table 2, patient 9) died on the first postoperative day of congestive heart failure. In this patient, the interval from M+M to MVR had been 1 day, during which time he had remained in congestive heart failure. The other 10 patients were discharged from the Clinical Center.

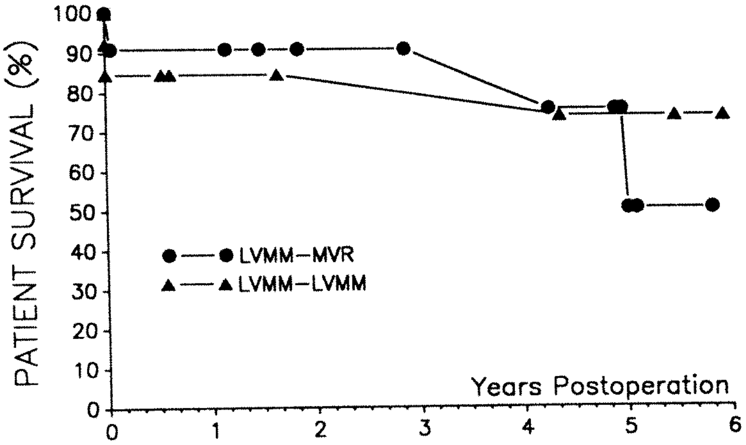
At 6 to 12 months postoperatively, 8 of the 10 hospital survivors were symptomatically improved and 2 were unchanged. The mean functional class after reoperation was significantly improved from that preoperatively (1.9 versus 3.3, $p < 0.05$). Eight of the 10 patients underwent postoperative cardiac catheterization, and in each of them, the left ventricular outflow obstruction was absent or trivial. The mean left ventricular outflow gradients at rest and with provocation (use of isoproterenol or other maneuver noted in Table 2) were significantly decreased from preoperative values whereas mean cardiac indices were unchanged. Two of the 10 hospital survivors died during the follow-up period: 1 of congestive heart failure 4.2 years postoperatively (Table 2, patient 10) and 1 of cancer after 4.9 years (Table 2, patient 4). Further mitral

Table 1. Clinical Findings in 12 Patients With Hypertrophic Cardiomyopathy Who Underwent LVMM Followed by a Second LVMM

			Catheterization Data Before First LVMM							Catheterization Data Before Second LVMM								Catheterization Data 6 Months After Second LVMM						
					LV-AO Gradients							LV-AO Gradients								LV-AO Gradients				
Patient No.	Age at First LVMM (y)	Sex	FC (1–4)	PA s/d	Resting	Provoked[a]	CI	MR (0–3)	Septum Resected (g)	FC (1–4)	PA s/d	Resting	Provoked[a]	CI	MR (0–3)	Age at Second LVMM (y)	Interval to Second LVMM (mo)	FC (1–4)	PA s/d	Resting	Provoked[a]	CI	MR (0–3)	Septum Resected (g)
1	8	F	2	18/10	150	. . .	2.5	2+	1.3	3	28/8	80	155	1.8	1+	22	168	3[c]	26/8	0	127	2.8	1+	0.7
2	19	M	3	50/25	6	80	1.1	3+	. . .	3	34/20	45	120	2.2	1+	24	37	5	. . .	. . .	. . .	. . .	. . .	0[d]
3	20	F	2	28/6	60	. . .	3.8	0	0[e,f]	3	23/6	80	205	1.9	1+	24	43	1	22/8	0	0[g]	3.6	. . .	3.5
4	22	M	3	28/16	62	136	4.5	1+	1.3	3	16/12	75	140	3.0	2+	22	4	3	17/9	15	40	3.4	1+	3.5[h]
5	25	M	3	. . .	120	140	2.2	. . .	1.0	2	. . .	50	120	2.7	. . .	26	19	1	. . .	20	40	2.2	. . .	0.6
6	30	M	3	. . .	. . .	. . .	. . .	. . .	. . .[f]	3	30/15	90	100	2.5	3+	40	69	2	32/14	40	94[g]	2.9	1+	1.4
7	31	F	3	29/18	55	91[h]	3.8	. . .	. . .[f]	4	24/10	42	78[i]	4.2	1+	34	38	2	. . .	. . .	. . .	. . .	. . .	1.5
8	33	F	3	. . .	50	. . .	. . .	1+	. . .[f]	3	50/20	75	. . .	4.7	2+	39	78	2	. . .	0	85	. . .	. . .	1.6
9	35	M	3	. . .	. . .	. . .	. . .	. . .	. . .[f]	3	30/10	65	160	3.4	1+	37	17	5[c,e]	. . .	. . .	. . .	. . .	. . .	0[d]
10	42	M	3	. . .	. . .	. . .	. . .	. . .	. . .[f]	2	30/20	40	115	2.0	1+	48	77	3[b]	23/13	30	90	2.9	1+	2.0
11	42	F	4	26/14	86	. . .	2.3	1+	. . .[f]	3	. . .	55	75	. . .	1+	43	10	2	. . .	0	0	3.4	2+	1.6
12	45	M	3	34/6	100	. . .	1.9	2+	2.0	4	55/35	80	. . .	. . .	3+	45	<1	1	36/21	20	40	. . .	1+	2.0[h]
Mean	29		2.8	29/13	75	111	2.7		1.4	3	31/15	65	125	2.7		33	46	2.5	25/11	13	57	2.9		1.9

[a] Gradient measured during infusion of isoproterenol unless otherwise noted. [b] Mitral valve replacement (without hospital death) was later performed for persistent left ventricular outflow obstruction. [c] Patient died before postoperative catheterization. [d] Fatal hemorrhage occurred before left ventricular myotomy and myectomy could be accomplished. [e] Myotomy not myectomy was performed. [f] First operation not performed at the National Institutes of Health. [g] Gradient measured during Valsalva maneuver. [h] Suture plication of the anterior mitral leaflet was performed in addition to left ventricular myotomy and myectomy. [i] Gradient measured during inhalation of amyl nitrite.

AO = aortic pressure (mm Hg); BS = Björk-Shiley (tilting disc); CI = cardiac index (L · min^{-1} · m^{-2}); F = female; FC = functional class (New York Heart Association); H = Hancock; LV = left ventricular pressure (mm Hg); LVMM = left ventricular myotomy and myectomy; M = male; MR = mitral regurgitation; MVR = mitral valve replacement; PA = pulmonary artery pressure (mm Hg); s/d = systolic/diastolic; SJM = St. Jude Medical.



Number of Patients at Risk

	0	1	2	3	4	5	6
LVMM–MVR	11	10	7	6	6	3	0
LVMM–LVMM	12	8	7	7	7	6	5

Fig 1. Actuarial survival curves, including hospital deaths, after reoperation for persistent left ventricular outflow obstruction after previous left ventricular myotomy and myectomy (LVMM) *in hypertrophic cardiomyopathy; 12 patients underwent repeat LVMM and 11 underwent mitral valve replacement* (MVR).

operations were required in 2 patients: 1 had closure of a perivalvular leak 7 months after MVR (Table 2, patient 10) and 1 had replacement of the prosthetic valve because of thrombosis 4.1 years after insertion (Table 2, patient 3). An actuarial survival curve of the 11 patients who underwent MVR after M+M is presented in Figure 1. Including the one hospital death, actuarial survival at 3 and 5 years was 92% and 77%, respectively.

Comment

This analysis of 23 patients who underwent reoperation for persistent left ventricular outflow obstruction after M+M in hypertrophic cardiomyopathy indicates that either a second M+M or MVR is effective in relieving the hemodynamic obstruction and in decreasing symptoms. Comparison of the second M+M group with the MVR group disclosed a significantly younger mean age at the initial operation (29 ± 11 years versus 40 ± 8 years, $p < 0.05$) and at reoperation (33 ± 10 years versus 42 ± 8 years, $p < 0.05$), a significantly longer time interval between operations (46 ± 43 months versus 18 ± 13 months, $p < 0.05$), and a significantly higher mean left ventricular outflow gradient with provocation (57 ± 44 mm Hg versus 14 ± 8 mm Hg, $p < 0.05$) after reoperation. Both groups showed similar improvement in functional class and in relief of left ventricular outflow obstruction at rest. Differences in hospital and late mortality after reoperation were insignificant.

Previous studies have compared the effectiveness of M+M and MVR at the initial operation for obstructive hypertrophic cardiomyopathy. Krajcer and associates [7] from Houston compared results of M+M in 127 patients with results of MVR in 58 patients. Early and late postoperative mortality were similar. Mitral valve replacement significantly lowered the mean left ventricular end-diastolic pressure, whereas M+M did not. Long-term symptomatic and hemodynamic improvement, however, were similar. Four of the 58 patients who had MVR had undergone previous M+M, but no description of outcome of these 4 patients was provided. Krajcer and associates concluded that most patients who require operative therapy should undergo M+M to avoid the disadvantages of valvar prostheses. Although our analysis concerned patients requiring reoperation, not initial operative therapy, our conclusion regarding the preferable procedure, M+M, is similar to that of Krajcer and associates.

A comparison of results of M+M and MVR was also recently reported by Walker and associates [4] from Edinburgh, Scotland. Eleven patients underwent M+M and 11 underwent MVR. One of the latter 11 patients had previously undergone M+M. Although both operations significantly reduced the left ventricular outflow gradient, the reduction was greater after MVR. Walker and associates also noted increased left ventricular cavity enlargement after MVR and suggested that this procedure was preferable in patients with mitral dysfunction or poor diastolic compliance. Our results at reoperation were similar in that the provokable left ventricular outflow gradient was significantly lower after MVR.

Persistent left ventricular outflow obstruction after M+M most commonly occurs because the M+M trough in the ventricular septum is inadequate in length, depth, or location. Intraoperative epicardial echocardiography has been used at our institution to characterize the trough after M+M. The length of the trough toward the apex is determined in the long-axis view; the depth of the trough and its circumferential location in the outflow tract are determined in the short-axis view. Mitral-septal contact with outflow obstruction may persist after M+M if the trough does not extend far enough apically, if the trough is not deep enough in the septum, or if the trough lies in a different circumferential location than the point of mitral-septal contact in the outflow tract.

From this retrospective analysis, we conclude that a second M+M is the preferred reoperative procedure in most patients with persistent left ventricular outflow obstruction because complications related to anticoagulation and substitute valves are avoided. Such complications occurred in 2 of the 11 patients who had MVR

Table 2. Clinical Findings in 11 Patients With Hypertrophic Cardiomyopathy Who Underwent Left LVMM Followed by MVR for Persistent Left Ventricular Outflow Obstruction

			Catheterization Data Before LVMM							Catheterization Before MVR										Catheterization Data 6 Months After MVR					
					LV-AO Gradients							LV-AO Gradients						Mitral Prosthesis				LV-AO Gradients			
Patient No.	Age at LVMM (y)	Sex	FC (1–4)	PA s/d	Resting	Provoked[a]	CI	MR (0–3)	Septum Resected (g)	FC (1–4)	PA s/d	Resting	Provoked[a]	CI	MR (0–3)	Age at MVR (y)	Interval LVMM to MVR (mo)	Type	Size	FC (1–4)	PA s/d	Resting	Provoked[a]	CI	MR (0–3)
1	29	F	3	22/12	70	145	2.5	2+	2.6	3	21/9	28	90	3.1	2+	30	16	BS	25	3	26/15	10	20	3.1	1+
2	31	F	3	20/10	60	75	3.0	1+	0.9	3	22/14	35	60	3.0	1+	35	47	SJM	23	2	24/14	0	15	3.4	1+
3	37	F	3	31/16	125	. . .	2.6	1+	1.3	3	23/9	60	100	2.8	1+	39	21	BS	23[b]	3	. . .	. . .	. . .	. . .	. . .
4	38	F	4	20/10	70	200	2.3	2+	1.0	3	29/13	10	140	1.8	1+	41	26	BS	23	2	48/20	0	0	2.2	0
5	39	M	3	30/12	90	125	2.1	1+	2.1	4	30/16	40	85	1.8	2+	41	20	BS	25	2	30/16	5	20	3.8	0
6	40	M	3	25/12	130	. . .	2.3	2+	2.3	4	23/10	10	108	2.6	1+	42	19	BS	27	2	30/16	0	20[c]	2.8	1+
7	41	F	3	27/12	85	90	2.2	1+	6.0	2	24/12	30	75	2.4	0	41	10	SJM	25	1	. . .	. . .	. . .	. . .	. . .
8	41	F	3	38/25	110	. . .	2.2	3+	3.0	4	35/22	140	. . .	2.4	. . .	41	<1	SJM	27	1	. . .	. . .	. . .	. . .	. . .
9	41	M	3	40/19	76	110	2.8	1+	2.8	4	40/20	40	. . .	1.5	. . .	41	<1	BS	25	5[d,e]	. . .	. . .	. . .	. . .	. . .
10	53	M	3	40/15	60	120	2.6	2+	2.3	4	37/22	50	90	3.5	0	54	20	BS	25[f]	2	38/18	0	4	2.5	0
11	58	M	3	22/10	80	100[g]	1.4	1+	2.2	3	25/7	50	80[g]	2.6	1+	60	24	BS	27	1	. . .	. . .	. . .	. . .	. . .
Mean	40		3.0	29/13	86	120	2.4		2.4	3.4	28/14	44	92	2.5		42	18			2.1	32/16	2.5	10	2.9	

[a] Gradient measured during infusion of isoproterenol unless otherwise noted. [b] Repeat mitral valve replacement for acute valve thrombosis was performed 4 years later. [c] Gradient measured during inhalation of amyl nitrite. [d] This patient died on the first postoperative day of congestive heart failure; the interval from left ventricular myotomy to mitral valve replacement was 1 day. [e] Patient died before postoperative catherization. [f] Closure of a peribasilar leak was performed 7 months after mitral valve replacement. [g] Gradient measured during Valsalva maneuver.

AO = aortic pressure (mm Hg); BS = Björk-Shiley (tilting disc); CI = cardiac index (L · $\text{min}^{-1} \cdot \text{m}^{-2}$); F = female; FC = functional class (New York Heart Association); H = Hancock; LV = left ventricular pressure (mm Hg); LVMM = left ventricular myotomy and myectomy; M = male; MR = mitral regurgitation; MVR = mitral valve replacement; PA = pulmonary artery pressure (mm Hg); s/d = systolic/diastolic; SJM = St. Jude Medical.

(Table 2, patients 3 and 10). Mitral valve replacement as a reoperative procedure can be justified, however, in severely symptomatic patients in whom (1) left ventricular outflow obstruction is mild and mitral regurgitation is severe; (2) the ventricular septum at the site of the trough is relatively thin, increasing the risk of ventricular septal defect in a second M+M; (3) the anterior mitral leaflet contacts the septum within an already deep trough; or (4) more than one previous M+M failed to relieve outflow obstruction.

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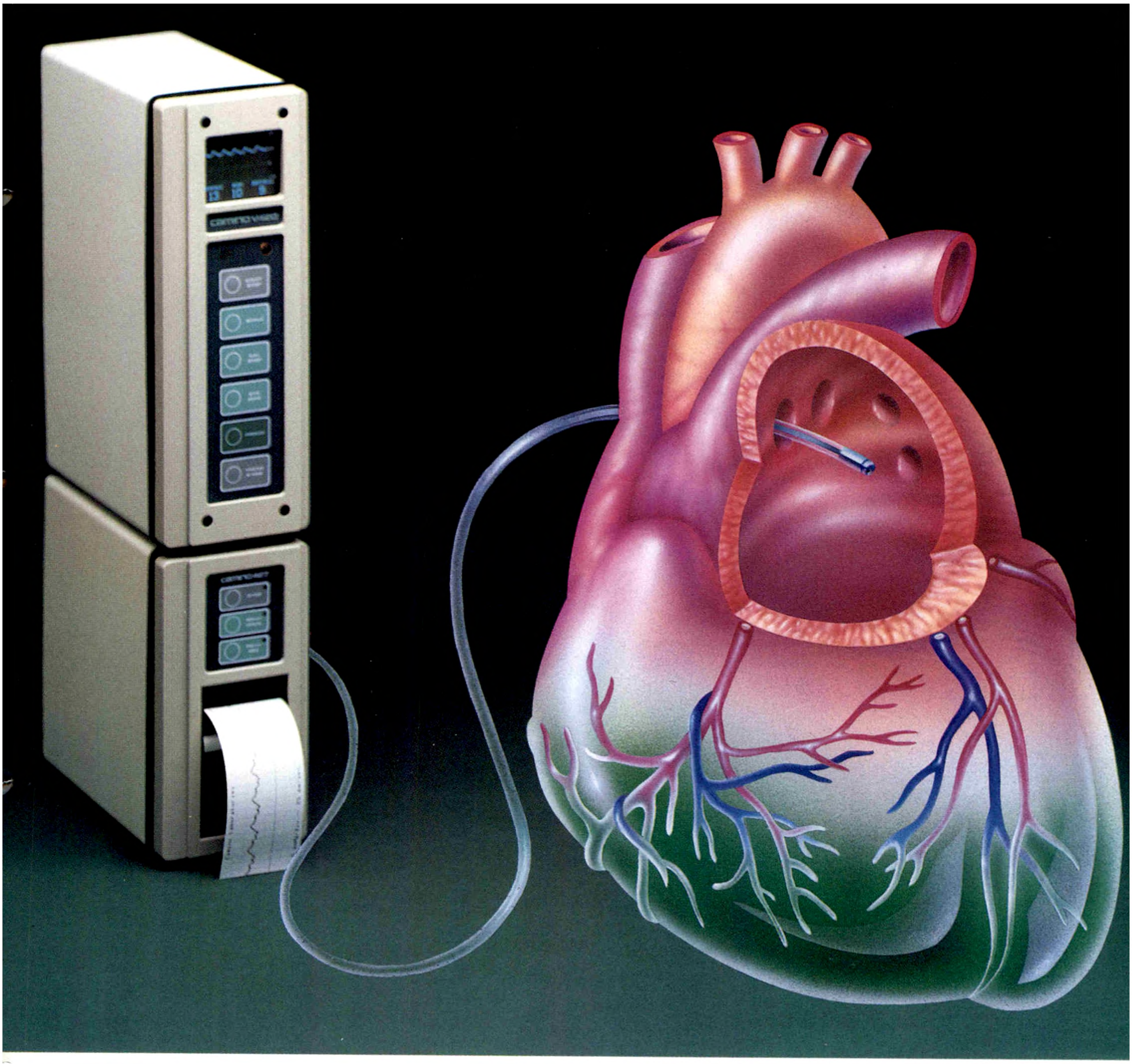

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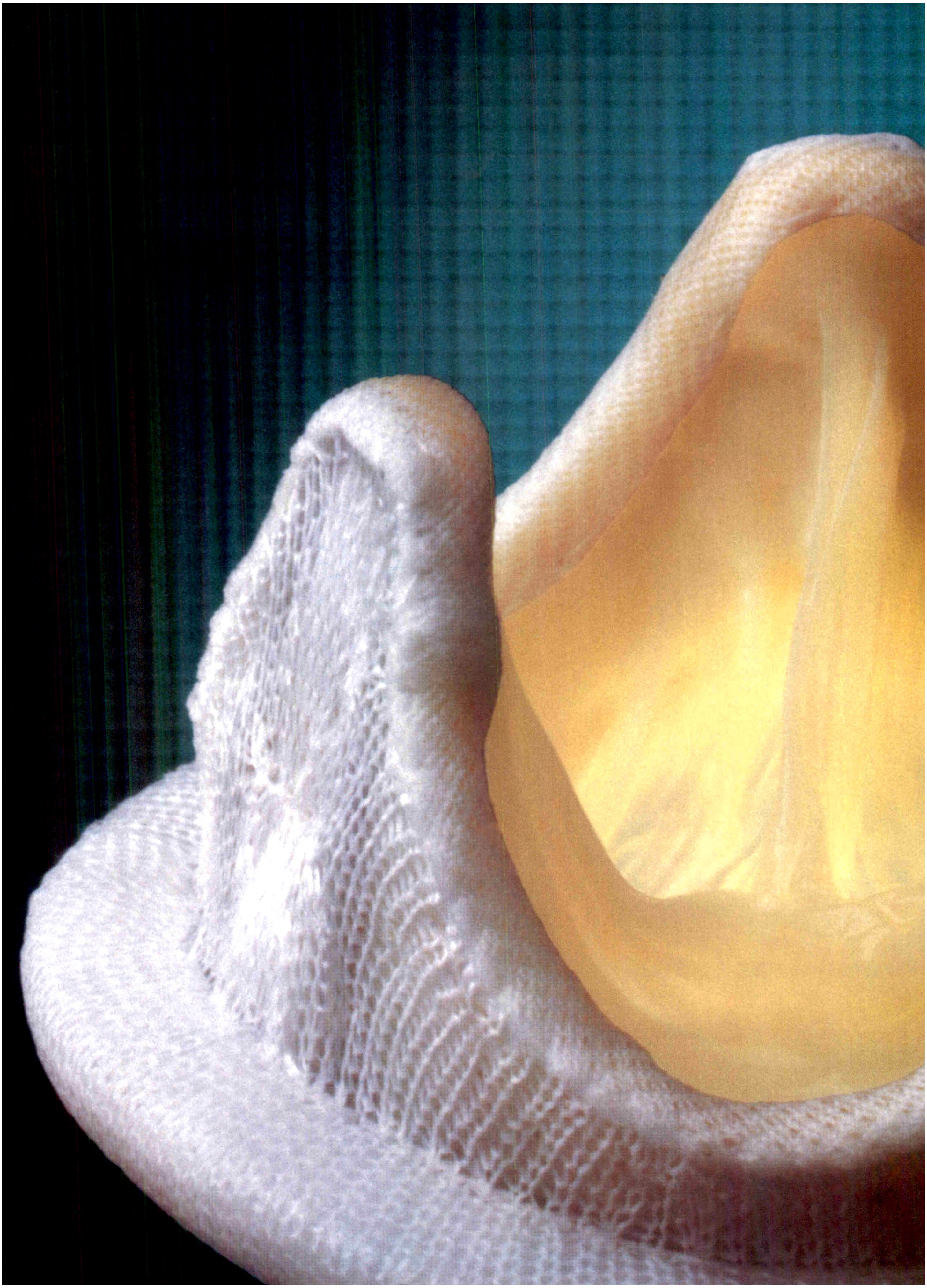

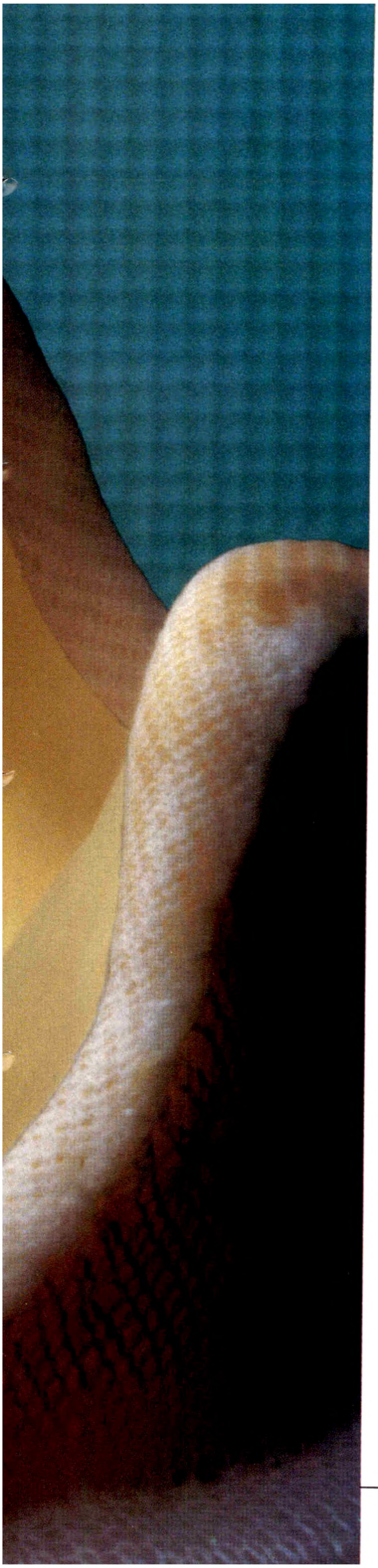

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The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient are made, and alternative methods of treatment are considered. Overall durability, especially long-term, has not been established for bioprostheses. Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery. **Note:** Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis. Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. The appropriate anticoagulation therapy must be determined by the physician on an individual basis. **Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result. The Carpentier-Edwards bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.** Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards bioprosthesis could damage the valve. Consequently, it is recommended that these procedures be avoided. Both the valve and glutaraldehyde storage solution are **sterile.** The outside of the jar is **not sterile** and must **not** be placed in the sterile field. Furthermore, the valve and container should **never** be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation. Storage between 10°C and 25°C is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue. **Any valve that has been frozen or exposed to temperatures greater than 60°C should not be used for human implantation.** Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with eyes, seek medical attention. **Surgical Precautions: 1.** When choosing a valve for a given patient, the size, age, and physical condition of the patient in relation to the size of the prosthesis must be taken into consideration to minimize the possibility of obtaining a suboptimal hemodynamic result. The selection of a valve, however, must ultimately be made by the physician on an individual basis after carefully weighing all of the risks and benefits to the patient. **2.** Due to the relative flexibility of the frame, care must be exercised to avoid the use of too large a prosthesis to prevent folding or extreme deformation of the stent that may render the valve incompetent. Oversizing may create highly localized mechanical stresses resulting in tissue failure in the form of detachment of the leaflets or porcine aortic wall from the valve stent posts. **3.** Left ventricular perforation or ulceration has been reported. Both open and closed chest cardiac massage in patients with an open strut mitral prosthesis increases the risk of ventricular perforation. Additionally, lifting, flexing, and manual compression of the distended heart after discontinuation of bypass may cause a commissure strut to be pushed through the endocardium, producing a dissecting hematoma with subsequent uncontrolled hemorrhage. **4.** The spacing of the sutures in the remnant of the valvular orifice and the prosthesis suture ring must be carefully matched to avoid folding of the leaflets or extreme distortion of the orifice. Edwards CVS Division has received reports in which individual mattress sutures, spanning a distance of 10 to 15mm, produced a purse-string effect causing compression of the valve orifice. **5.** When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue. Cases have been reported in which bioprostheses developed severe regurgitation and had to be replaced as a result of wear due to contact with sutures. **6.** Unlike rigid mechanical valves, the stent wall is soft and will not resist needle penetration. Accordingly, extreme care must be exercised when placing sutures through the sewing margin to avoid penetration of the side wall of the stent and possible laceration of the leaflet tissue. **7.** As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised, particularly in mitral replacement, to avoid looping or catching a suture around the free legs which would interfere with proper valvular function. **8.** The stent of the bioprosthesis is asymmetrical to conform to the natural shape of the porcine aortic valve. Consequently, the commissure supports are not equidistantly spaced. The contrasting suture markers in the sewing ring of the mitral valve denote the greatest intercommissural distance. These two commissure supports should be oriented so as to straddle the ventricular outflow tract to avoid murmurs due to blood flow turbulence. **Note:** The contrasting suture material should not be removed from the prosthesis. **9.** In the aortic position, the struts should correspond to the remnants of the natural commissures so as not to obstruct the coronary ostia. **10.** A serial number tag is attached to the sewing ring of each valve by a suture. This serial number should be checked against the number on the jar; if any difference is noted, the valve should be returned unused. This tag should not be detached from the valve until implant is imminent. Care should be exercised to avoid cutting or tearing the suture ring cloth during removal. **11.** Gentle handling is required for all implantable devices. If the valve is dropped, damaged, or mishandled in any way, it must not be used for human implantation. **Complications:** As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Complications associated with the use of Carpentier-Edwards bioprostheses include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct. **Note:** Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes an apparent causal relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards bioprostheses to calcification as compared to other commercially available porcine valves. **Caution:** Federal (USA) law restricts this device to sale by or on the order of a physician. Baxter International Inc. is the owner of the following US patent which covers the products described herein: 4,106,129. Patent numbers in foreign countries supplied upon request. See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information. Carpentier-Edwards® is a registered trademark of Baxter International Inc.

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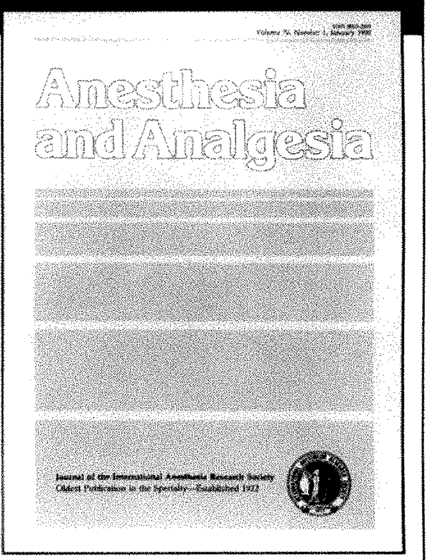

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Thoracoscopic Debridement and Pleural Irrigation in the Management of Empyema Thoracis

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As a sequel to a paper reporting good results obtained in 12 patients with empyema thoracis treated by thoracoscopic debridement and irrigation in our department, subsequent experience with a further 18 patients is reported. Drainage of pus and irrigation resulted in resolution of pyrexia with improvement in general condition in all patients. Overall, complete resolution was obtained by this technique alone in 60% (18/30). Of the 12 patients in whom complete resolution was not obtained, secondary surgical measures resulted in resolution of empyema in 8. Four patients died; all were elderly and severely debilitated, 3 with advanced malignancy. Their deaths were not related to the technique, which was well tolerated in all cases. Thoracoscopic debridement and irrigation used routinely as a first-line measure in empyema thoracis is a safe and relatively atraumatic procedure, does not exclude the use of any subsequent surgical measure, and provides valuable time to improve the condition of debilitated patients so that they may tolerate more aggressive surgical procedures.

(Ann Thorac Surg 1991;51:461–4)

With the advent of effective antibiotic treatment, the incidence of empyema thoracis has decreased [1] and the responsible pathogens have altered [2, 3]. However, empyema remains a condition with substantial morbidity and mortality [4].

The most effective treatment of empyema thoracis remains controversial. Most cases are treated initially under the care of chest physicians by repeat aspiration (thoracentesis) or insertion of an intrapleural underwater seal drain (closed thoracostomy). Some selected empyemas can be satisfactorily treated with such conservative regimens alone [5]. Traditional surgical approaches include rib resection and open drainage [4], open window thoracostomy [6, 7], decortication [8], and thoracoplasty [9, 10]. More recently thoracoscopy and cyclical irrigation of the thoracic cavity have been described [11].

Initially we employed thoracoscopic debridement and irrigation in a select group of patients with empyema excluding those with complications, severely debilitated patients, and those with bronchopleural fistulas. This selection resulted in 100% success in a consecutive series of 12 cases, including 1 tuberculous empyema and patients with symptoms of up to 3 months' duration [12]. As a result, the technique has been used as first-line treatment for all cases of empyema thoracis.

Patients and Methods

Technique of Thoracoscopic Debridement and Irrigation

A modification of Rosenfeldt's technique [11] as described by Hutter and associates [12] was used. General anesthesia was employed. A double-lumen tube allowed the lung on the affected side to collapse, improving visualization of the empyema cavity, and was employed in all cases except 1, in which the patient had had a previous pneumonectomy and empyema developed on the side of his remaining lung; a long single-lumen tube was used in this case. Inflating the cuff around the endobronchial tube to the good lung is important to protect against spillage from the empyema cavity in the event of a bronchopleural fistula.

With the patient in the lateral position sterile drapes were placed and a Saugmann's needle (GU Instruments, London, England) was inserted into the empyema cavity to determine its extent and locate a dependent site where the lung was displaced from the chest wall and unlikely to be injured by instrumentation. A standard laparoscope (Jacobs-Palmer Fiber Light Operating Laparoscope FW4937-V; Richard Wolf Ltd, Mitcham, Surrey, England) [13] was inserted to visualize the extent of the empyema cavity. Typically, the site of insertion was the fifth intercostal space in the posterior axillary line. The laparoscope is a major improvement over standard thoracoscopy equipment [4] because of its large bore, which allows better debridement, its superior lighting and field of view, and its offset parallel eyepiece, which allows easier and direct manipulation of the biopsy forceps and suckers.

With the tip of the laparoscope, loculi and adhesions were broken down under direct vision. Then the instrument was removed but the cannula was left in position and the cavity was thoroughly irrigated to remove all fibrinous fragments. Full debridement was possible owing to the wide bore of the laparoscope cannula, any debris becoming lodged in the cannula being readily removed with long-handled forceps. Thoracoscopy was repeated and areas of debris remaining were dislodged with the instrument tip and forceps. Irrigation was continued until the cavity was clean. Empyema fluid was sent

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for culture and pleural biopsy specimens were taken through the laparoscope.

Under direct vision a 12F Argyle drain was placed apically to infuse the irrigation fluid and the laparoscope was replaced by a basal 32F Argyle drain, which fitted the hole made by the laparoscope trocar without leakage around it. Sideholes cut in the basal drain allowed drainage over a 15-cm length of tube, with the lowest hole 2.5 cm inside the parietal pleura. The advantage of the Argyle drain is that at 37°C it is supple and is tolerated intercostally for weeks if necessary. Early rib resection, mandatory with stiffer tubing, becomes unnecessary. If open tube drainage subsequently becomes necessary, this can sometimes be achieved by simply shortening the basal drain without rib resection.

The empyema cavity was irrigated twice daily, once with 1% noxythiolin solution and once with normal saline solution. Drainage fluid was collected and cultured daily, and after three consecutive sterile cultures, irrigation was discontinued and the drains were removed. The primary objective of the procedure was to sterilize the thoracic cavity as soon as possible.

Patients

All patients undergoing thoracoscopic debridement and irrigation of empyema thoracis between August 1984 and August 1988 were retrospectively reviewed. Diagnosis was established by the evacuation of frank pus from the pleural cavity with or without positive culture. The cause, method of management, and eventual outcome were recorded in each patient.

Results

During the 4-year period of the study 18 patients (10 male) were treated. Their ages ranged between 15 and 82 years, with a mean age of 57.

Cause

Sixteen patients were referred after initial management by respiratory physicians. The most common precipitating factor was pneumonia, which was responsible for empyema in 14 (5 of whom had a bronchopleural fistula). In 2 patients, both of whom died, local invasion of advanced malignancy was responsible for empyema. None of these 16 patients was seen de novo and all had major chest instrumentation (closed thoracostomy in 9, repeat thoracentesis in 7) without resolution of the empyema before referral to our department.

Recent surgical procedures caused empyema in 2 cases. In 1, the patient had chronic renal failure requiring hemofiltration and had recently undergone a talc pleurodesis with subsequent empyema. In another debilitated paraplegic patient an infected pleural space developed after a left upper lobectomy for malignant disease.

Outcome

THORACOSCOPIC DEBRIDEMENT AND IRRIGATION ALONE. Of the 18 patients, complete resolution of empyema was achieved by thoracoscopic debridement and pleural irrigation alone in 6/18 (33%) who had no evidence of bronchopleural fistula and were not grossly debilitated. Irrigation was continued for a mean period of 10.7 (±1.0) days. Three consecutive sterile cultures were obtained in these patients before removal of the drains and none had recurrence of empyema.

Two patients died while irrigation was still in progress. One, a 67-year-old man with advanced bronchial carcinoma invading the chest wall, died of myocardial infarction 14 days postoperatively; the other, an 82-year-old man who had previously had a pneumonectomy for carcinoma of bronchus, had pneumonia of his remaining lung with empyema formation and died of myocardial infarction 12 days postoperatively.

Combining this series with Hutter and associates' [12] earlier series of 12 patients gives a departmental experience of 30 patients in whom complete resolution was obtained by this technique alone in 18/30 (60%).

SECONDARY SURGICAL MEASURES. Ten patients proceeded to secondary surgical measures when the initial management with thoracoscopic debridement and pleural irrigation failed to sterilize the cavity and resolve the empyema: 5 were treated with open tube drainage, 2 by decortication, 2 by Eloesser flap, and 1 with a rectus abdominis flap. Resolution of the empyema was achieved in 8 of the 10 and 2 patients died before leaving the hospital.

In 4 of the 5 patients who were treated with chronic open tube drainage as second-line treatment, a bronchopleural fistula had become apparent when the patient noticed the salty taste of the saline irrigation fluid. Four patients had a standard rib resection and insertion of a large-bore tube. In the other patient simply cutting short the basal irrigation drain without rib resection provided satisfactory open drainage. Open drainage was followed by management as an outpatient and in all 5 patients the empyemas eventually resolved. The management of open tube drainage of empyema thoracis is made considerably less troublesome to the patient and his or her relatives by the use of modern stoma bags and the experience of a nurse trained in stoma care. These patients were followed up in the outpatient clinic where they were seen by both the consultant surgeon and the stoma care nurse on the same day [14].

Decortication was employed as the second-line treatment in 2 patients (aged 18 and 19 years) with chronic empyemas with extensive fibrous tissue. Both tolerated the thoracotomy uneventfully and made a complete recovery.

Open drainage with an Eloesser flap procedure [15] was used in 2 patients. In one, a debilitated 74-year-old man with empyema necessitatis, resolution was achieved after prolonged outpatient management. The other, a debilitated 80-year-old woman with advanced rheumatoid arthritis, a large gastric ulcer, and severe anemia, had an empyema associated with a bronchopleural fistula. After formation of an Eloesser flap she was initially stable but suffered further gastric blood loss and died 14 days later.

After thoracoscopy and pleural irrigation, a rectus abdominis flap was swung to fill the defect of a 75-year-old woman with advanced breast malignancy directly invading the chest wall and causing osteomyelitis of the sternum and empyema. She died of a pulmonary embolus immediately after the procedure.

Comment

It has long been customary to describe empyema clinically as either "acute" or "chronic." Many of today's patients are old and debilitated with severe associated disease so that it is difficult to estimate the duration of their disease. A more satisfactory pathological definition of "acute" and "chronic" is that of Barrett [16], who defined an acute empyema as one in which the pleura is lined by infected fibrin, whereas in chronic empyema the fibrin has changed to fibrous tissue. However the transition from a thin-walled, fibrin-covered cavity containing thin pus to a thick, fibrous-walled cavity containing viscous pus represents a spectrum of pathological conditions. The patient may be seen at any stage of the condition. Most of the patients in this series were referred at a late stage after initial treatment with repeat thoracentesis or closed thoracostomy and were therefore relatively chronic with multiple pleural adhesions in all cases.

The nature of any infecting organisms did not affect outcome, and they are therefore not discussed in this paper. Antibiotics, although of value in the treatment of pneumonia and thus reducing the incidence of empyema, are of no proven value in the management of established empyema [3]. The technique of thoracoscopy and irrigation emphasizes the importance of mechanical removal of infected and potentially infected material together with the breakdown of pleural adhesions and loculated pus to encourage reexpansion of the underlying lung. Reexpansion of the lung reduces the size of the empyema space and improves chances of resolution, but the essential requirement and aim of this procedure is sterilization with or without obliteration of the empyema space.

Intercostal drainage alone frequently fails as there is no debridement of fibrin plugs in the pleural cavity, loculi of pus are not broken down, and drainage is not dependent, allowing a pool of pus to collect below the site of drain insertion. Cyclical irrigation of the pleural cavity has been shown to be a more effective method of removing pus from the pleural cavity [12, 17]. The use of the thoracoscope to visualize the pleural cavity directly, debride pleural adhesions, and break down loculated pus enhances the efficacy of subsequent irrigation.

The technique of thoracoscopic debridement and cyclical irrigation imitates the essentials of rib resection and drainage but has the advantage of closed thoracostomy drainage in that it is less traumatic and does not compromise subsequent surgical interventions as can be the case with rib resection and open drainage. As in rib resection, early, adequate, and "dependent" drainage is achieved. The technique can be employed early as well as at late stages of the empyema and does not have to be delayed until the pleura has adhered. It is particularly suitable for children and primary referral and may avoid the tendency to chronicity and prolonging resolution after failed medical management. With modern techniques even old and debilitated patients can tolerate general anesthesia. Physicians can refer early with confidence because of the relatively minor surgical procedures involved. Drainage is adequate because fibrin, which tends to block drains, is removed and loculi are broken down. A large 32F Argyle plastic basal drain is placed accurately at the base of the empyema cavity but a completely dependent site is unnecessary as repeated irrigation washes out any pus below the site of drain insertion. Unlike rubber drains, the Argyle plastic drain accommodates comfortably and allows prolonged intercostal drainage. The two percutaneously inserted drains are only required during the period of cyclical irrigation. The patient can leave the hospital immediately after their removal without dressings, unlike rib resection and drainage, which typically requires regular dressings for 6 months after the procedure.

In the 5 patients who had bronchopleural fistulas, it was not possible to sterilize the pleural space. However, by using lower volumes of irrigation fluid and altering the position of these patients, it was possible to continue irrigation until their general condition was improved, making them better able to tolerate secondary surgical measures. Therefore, preoperative evidence of a bronchopleural fistula, such as copious productive cough or a fluid level on chest roentgenogram, should not be considered a contraindication to this technique although in such cases the empyema is unlikely to be resolved with this technique alone.

In the first, select group of 12 patients treated in this department with thoracoscopic debridement and irrigation and reported by Hutter and associates [12], the technique achieved resolution in all patients. Subsequently the technique was extended to all cases of empyema thoracis and, as expected, the number of patients in whom complete resolution was obtained by this technique alone decreased. Patient selection is therefore shown to be a major determinant of outcome. Failure to achieve complete resolution by thoracoscopic debridement and irrigation alone was associated with bronchopleural fistulas, empyemas at the chronic end of the pathological spectrum, and malignancy or other serious disease (eg, renal failure, myocardial infarction).

Clearly there is no "correct" treatment for empyema. A number of treatment modes have advocates [4–10], all of which may have a place depending on the condition of the individual patient. We continue to use thoracoscopic debridement and irrigation as a first-line treatment in empyema thoracis, as the technique is safe and relatively atraumatic. It is well tolerated and produces rapid drainage of pus with resolution of pyrexia and associated toxemia. Should this technique fail to resolve the empyema, it does not exclude the use of further surgical measures and, in debilitated patients, it allows improvement of the patient's general condition before proceeding to further surgical management.

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INVITED COMMENTARY

A 60% success rate with the use of thoracoscopic debridement of empyema cavities in 30 patients is reported. However, this includes results with 12 previously reported, very carefully selected, patients wherein the use of the method was apparently helpful in all cases. Therefore, among 18 subsequent patients, in whom the indications for thoracoscopic management became more liberal, 10 patients required secondary procedures: 7 open (tubes or Eloesser flap) drainages, 2 decortications, and 1 rectus abdominis flap. It could therefore be argued that definitive treatment was delayed by the use of thoracoscopic debridement in 10 of 18 (more than half) of the most recently treated patients. This argument almost certainly applies to at least 2 patients, aged 18 and 19 years, who came to decortication; these patients probably had their illness prolonged by the attempt to use thoracoscopic debridement, instead of decortication, as the "first-line" surgical management. Ridley and Braimbridge have presented evidence that there is a place for thoracoscopic debridement in the treatment of empyema; the proper place remains to be established. In some cases, I am sure, the most conservative management will continue to be prompt open drainage or decortication by thoracotomy.

Nowhere in medicine is experience more useful in making judgments than in the treatment of empyemas. Many (perhaps most) patients with empyema come first to the attention of internists, including some physicians who regularly place chest tubes. Generally these physicians have had no opportunity to see the thick fibrinous exudate of many empyemas or to see a trapped lung. It should be reiterated that the first line of management for empyemas is to obtain consultation from an experienced general thoracic surgeon.

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Computed Tomography–Guided Minithoracotomy for the Resection of Small Peripheral Pulmonary Nodules

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Small peripheral pulmonary nodules ranging in size from 1 mm to 20 mm were excised in 58 patients. Computed tomography was used to mark the skin overlying the nodules to minimize the surgical exposure needed for operative identification. The nodules were 1 cm or less in maximum diameter in 76% of the patients. Twenty-six patients had single nodules and 32 patients had multiple nodules. The preoperative diagnosis was inaccurate in 67% of the patients. In 61% of the patients in whom malignancy was suspected, no tumor was demonstrated. Conversely, of the 20 patients in whom a malignant nodule was excised, the preoperative diagnosis was correct in only 50%. Thirty-one patients required no further treatment apart from their biopsy and 27 required additional intervention. Small peripheral pulmonary nodules require biopsy for diagnosis. When percutaneous needle aspiration biopsy is unsuccessful, or technically difficult, a computed tomography–guided thoracotomy is an effective and minimally invasive surgical alternative.

(Ann Thorac Surg 1991;51:465–9)

Successful percutaneous needle aspiration biopsy of peripheral pulmonary nodules is not always possible because of small nodule size or inaccessible location. Furthermore, in cases with complex histology, sufficient material for definitive diagnosis may not be obtained. In 1983, we described a computed tomographic method to locate small peripheral nodules permitting their excision with a guided minithoracotomy [1]. The present report

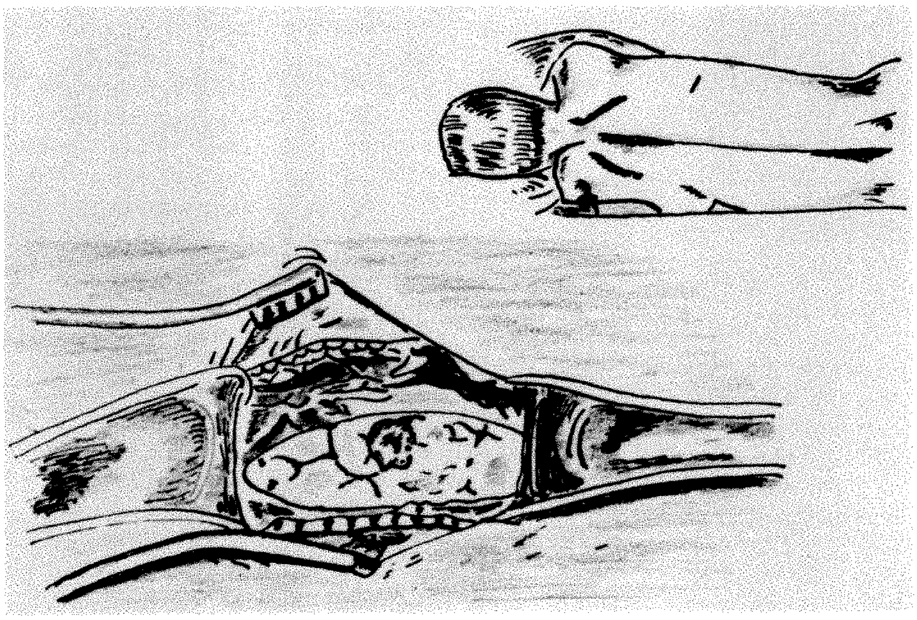

Fig 1. Operative exposure of a subpleural nodule. A small McBurney retractor at each pole of the incision spreads the ribs sufficiently to permit resection.

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Table 1. Patients With Single Nodules

Patient No.	Age (y)	Sex	Size (mm)	Lobe Biopsied	Preop Diagnosis	Postop Diagnosis
1	70	M	6	LLL	Metastasis	Lymph node
2	46	M	4	RML	Metastasis	Lymph node
3	65	M	9	RML	Metastasis	Hamartoma
4	56	M	6	LUL	Granuloma	Granuloma
5	56	F	10	LLL	Lung cancer	Lymph node
6	66	M	12	LLL	Pleural-based scar	Lung cancer
7	66	M	10	RLL	Lung cancer	Aspiration pneumonia
8	55	M	10	LUL	Metastasis	Lung cancer
9	76	F	5	LUL	Metastasis	Granuloma
10	68	M	15	RLL	Metastasis	Metastasis
11	58	M	8	RLL	Lung cancer	Hamartoma
12	41	M	9	LUL	Granuloma	Histoplasmosis
13	63	M	12	LLL	Hamartoma	Hamartoma
14	67	M	5	LUL	Lung cancer	Pulmonary scar
15	76	F	10	LUL	Granuloma	Pulmonary Hodgkin's
16	61	F	6	RML	Granuloma	Lymph node
17	54	M	7	LLL	Granuloma	Pulmonary infarct
18	53	M	17	RLL	Hamartoma	Pneumonitis
19	67	F	11	RLL	Lung cancer	Lung cancer
20	50	M	1	LLL	Granuloma	Scar
21	68	M	6	RLL	Lymph node	Lymph node
22	60	M	6	RLL	Hamartoma	Hamartoma
23	41	F	7	RLL	Histoplasmosis	Lymph node
24	39	M	10	LLL	Lung cancer	Hamartoma
25	51	F	7	RUL	Hamartoma	Hamartoma
26	71	M	13	LUL	Lung cancer	Lung cancer

LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

summarizes our experience with this technique in 58 consecutive patients with one or more small peripheral pulmonary nodules of unknown cause in whom computed tomography (CT)–directed percutaneous needle aspiration biopsy was considered technically difficult, inappropriate, or had been unsuccessfully attempted. In every patient, a definitive histological diagnosis was made by excisional biopsy using our CT–directed minithoracotomy approach.

Material and Methods

Twenty-six patients had single nodules on chest CT scan and 32 patients had multiple nodules. The median age was 61 years for patients with single nodules and 54 years for those with multiple nodules. There were 39 men and 19 women. Seventy-six percent of the patients in this series had nodules 1 cm or less in maximum transverse diameter on CT scan.

Patients selected for a CT–directed excisional biopsy were positioned in the gantry of the CT scanner in the position selected for operative exposure. The nodule to be resected was localized at total lung capacity. A barium marker was placed on the skin over the nodule and a repeat scan was obtained to confirm the surface localization. A dye marker then replaced the barium marker.

In the operating room, a 5-cm incision was made near the marker adjusting for the anticipated retraction of the lung on opening the pleura. The incision was carried directly down over the appropriate interspace without undercutting the margins of the incision and the ribs were gently separated with two small retractors at each end of the incision (Fig 1). The anesthesiologist adjusted lung volume to bring the nodule to the incision. The nodule was identified and excised using a stapler or sutures [2]. All lobes can undergo biopsy and are equally accessible. For apical lesions, we sometimes collapsed the lung using a double-lumen endotracheal tube and brought the nodule to the axilla. There was no mortality, one wound infection, and one air leak longer than 7 days. In the majority of patients the chest tube was removed by the third day and the patient was discharged. Patients rarely complained of substantial postthoracotomy pain.

Results

This procedure permitted accurate localization and surgical excision of nodules in all instances (Tables 1, 2). Twenty of the 26 patients with single nodules and 24 of the 32 patients with multiple nodules had lesions that were 1 cm or less in maximum transverse diameter on CT. Six of the patients with multiple nodules had lesions that

Table 2. Patients With Multiple Nodules

Patient No.	Age (y)	Sex	Size (mm)	Lobe Biopsied	Preop Diagnosis	Postop Diagnosis
1	27	M	12	RML	Metastasis	Granuloma
2	48	M	8	LUL	Metastasis	Pulmonary Hodgkin's
3	34	M	20[a]	RML	Hypersensitivity pneumonitis	Hypersensitivity pneumonitis
4	23	M	10[a]	LLL	Drug-induced pneumonitis	Metastasis
5	55	M	13	RLL	Lung cancer	Hamartoma
6	38	M	5	RML	Metastasis	Eosinophilic granuloma
7	67	M	10	LLL	Metastasis	Metastasis
8	47	M	3	LLL	Pulmonary Hodgkin's	Pulmonary Hodgkin's
9	49	M	5	RUL	Pleural-based scar	Metastasis
10	50	M	4[a]	RML	Granuloma	Histoplasmosis
11	48	M	6	RUL	Metastasis	Metastasis
12	74	M	6	LUL	Pleural-based scar	Metastasis
13	54	F	20	RML	Wegner's	Wegner's
14	58	F	6	LUL	Metastasis	Metastasis
15	49	F	2	RML	Chronic interstitial fibrosis	Primary lung cancer
16	64	F	13	RLL	Wegner's	Wegner's
17	64	M	4	RLL	Metastasis	Eosinophilic granuloma
18	82	F	2	LLL	Metastasis	Metastasis
19	43	F	5	RLL	Granuloma	Metastasis
20	69	M	8	RLL	Metastasis	Lymph node
21	63	M	4	RML	Metastasis	Lymph node
22	69	M	15	LUL	Metastasis	Lymphoma
23	54	F	7	RLL	Lung cancer	Pulmonary infarct
24	75	M	10	RUL	Wegner's	Wegner's
25	53	F	10	RUL	Metastasis	Eosinophilic granuloma
26	25	F	10	RUL	Metastasis	Metastasis
27	67	M	10	LUL	Metastasis	Granuloma
28	43	M	15	RML	Fungus	Wegner's
29	58	F	2	RML	Metastasis	Pneumonitis
30	63	M	5	RLL	Pneumonitis	Lymph node
31	30	F	4	LLL	Hodgkin's	Lymph node
32	25	F	4	RLL	Metastasis	Metastasis

[a] Size as measured by computed tomography (size not recorded by pathologist).

LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

were both less than and greater than 1 cm. The sizes of the excised nodules measured on cut section are seen in Table 3. Seventeen of the excised nodules were 5 mm or less in diameter and 45 were 1 cm or less in diameter. The histopathological diagnoses of the single nodules were as follows: intrapulmonary lymph node, 6; benign tumor, 6; primary lung cancer, 4; pulmonary scar, 2; granuloma, 2; and aspiration, metastasis, histoplasmoma, Hodgkin's disease, lymphocytic interstitial pneumonia, and nonspecific pneumonia, 1 each. The histopathological diagnoses of the excised nodules in the multiple-nodule group were as follows: metastases, 10; Wegner's granulomatosis, 4; intrapulmonary lymph node, 4; eosinophilic granuloma, 3; granuloma, 2; Hodgkin's disease, 2; and hypersensitivity pneumonitis, benign tumor, histoplasmoma, primary lung cancer, pulmonary lymphoma, pulmonary infarct, and nonspecific pneumonia, 1 each.

In only 9 of the 26 patients with single nodules (35%) and in only 12 of the 32 patients with multiple nodules (38%) was the preoperative clinical diagnosis correct. In

Table 3. Maximum Diameter of the Excised Nodule on Cut Section[a]

Variable	Single-Nodule Group	Multiple-Nodule Group	Combined Group
Median (mm)	9	7	8
Range (mm)	1–17	2–20	1–20
No. ≤5 mm	4	13	17
No. 6–10 mm	16	12	28
No. >10 mm	6	7	13

[a] Four of the nodules were measured by computed tomographic scan when size was not recorded by pathologist.

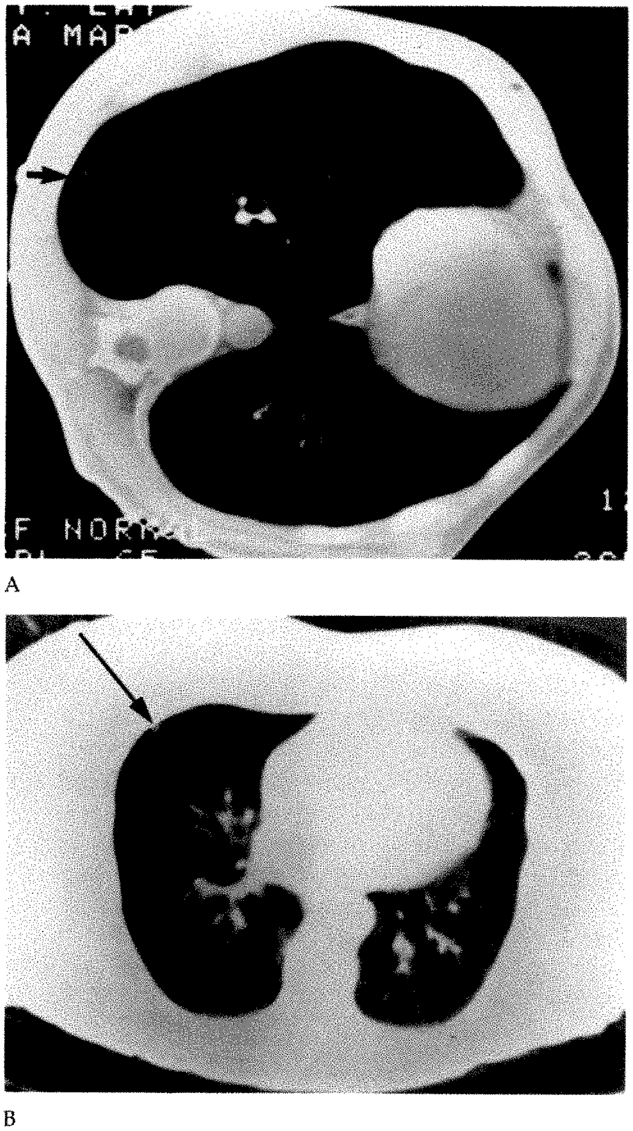

Fig 2. (A) A small peripheral pulmonary nodule (arrow) *is localized on the skin surface with a barium marker. The patient is in the left lateral decubitus position in the scanner. The nodule proved to be a metastasis. (B) A small peripheral pulmonary nodule* (arrow) *is localized with the patient supine. This nodule proved to be a subpleural lymph node.*

only 13 of the 33 patients with a preoperative diagnosis of primary or metastatic malignancy was a malignant diagnosis confirmed. The accuracy of a preoperative diagnosis of malignancy in patients with single nodules was only 31% and with multiple nodules, only 45%. Conversely, 20 of the 58 patients were proved to have malignancy on histopathological examination. In 65% of this group, malignancy was suspected preoperatively, but in only 10 of 20 patients or 50% was the precise malignant diagnosis suspected. Nodule size was of no help in distinguishing benign from malignant lesions. Whereas the malignant nodules ranged in size from 2 mm to 1.5 cm, benign intrapulmonary lymph nodes ranged in size from 4 mm to 1.0 cm. As an example, a pulmonary metastasis and a benign intrapulmonary lymph node are shown in Figure 2.

Thirty-one of the 58 patients received no treatment apart from their biopsy, and in the majority of these, the biopsy was definitive management. The remaining 27 patients received treatment directed by the biopsy. Eleven patients received chemotherapy, 8 required definitive operation, and in 2 of these the definitive operation was carried out under the same general anesthesia. Four patients required corticosteroids; 3, radiation therapy; and 1, antibiotics.

Comment

Thirty-four percent of the patients in this series with small single or multiple pulmonary nodules proved to have malignancy. On the other hand, only 40% of the patients with a preoperative diagnosis of malignancy proved to have a malignant lesion. In addition, 47% of the patients in this series required a specific therapeutic intervention based on the biopsy results. Our findings clearly indicate that newly detected small pulmonary nodules seen on chest CT scan should undergo biopsy. When feasible, percutaneous needle aspiration using CT guidance can often provide a definitive diagnosis [3]. When the nodule is malignant, the yield is relatively high and in cases of metastatic disease no additional invasive procedure is usually needed. On the other hand, when the lesion is benign the likelihood of a specific diagnosis after needle aspiration is significantly lower [4, 5].

The technique used in our patients entails minimum risk and a minimal period of convalescence. Furthermore, the surface localization of the nodules aids in their intraoperative identification especially when the nodules are small (<5 mm), because they may be difficult to palpate. In our experience, a CT-guided thoracotomy has provided a better alternative than follow-up reimaging with CT to determine the stability of the lesion. Appropriate treatment can be started promptly and excisional biopsy is often definitive therapy when the lesion is benign.

In conclusion, small peripheral pulmonary nodules should not be ignored. A definitive diagnosis should be obtained by either percutaneous needle aspiration or excision. The CT-guided minithoracotomy technique used in this series is a minimally invasive surgical alternative to follow-up imaging when percutaneous needle aspiration biopsy is impossible or when complex histology is suspected on clinical grounds.

We thank Lisa Doucette for her assistance in preparing this report.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1993 may begin the recertification process in 1991. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1991. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Combined Myocardial Revascularization and Abdominal Aortic Aneurysm Repair

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Myocardial infarction remains the leading cause of early and late deaths after abdominal aortic reconstruction in patients with abdominal aortic aneurysm. Our approach for the past 4 years has been combined myocardial revascularization with abdominal aortic aneurysm repair in patients with good left ventricle performance. From July 1984 through June 1989, 128 patients underwent abdominal aortic aneurysm repair. Seventeen patients underwent combined abdominal aortic reconstruction with coronary artery bypass grafting. One patient died (5.9%). The remaining patients are all well at current follow-up. Our experience shows that patients with coronary artery disease and abdominal aortic aneurysm may have both lesions safely repaired as a single operative procedure.

(Ann Thorac Surg 1991;51:470–2)

Surgical repair of an abdominal aortic aneurysm (AAA) has become a common procedure with an attendant low operative morbidity and mortality. It is well known that there is a high incidence of coronary artery disease in patients with AAA [1, 2]. Although the actual influence of coronary artery disease on operative mortality is not known, because of conflicting reports in the literature, it is known that late survival after aneurysm repair seems to be directly influenced by coronary artery disease [3, 4]. Aneurysm repair poses a major stress on the myocardium that may be accentuated by the presence of coronary artery disease [5, 6]. Since 1984 at our department we have combined myocardial revascularization with AAA repair in all patients who are believed to be hemodynamically stable.

Material and Methods

From July 1984 through June 1989, 128 patients underwent elective or urgent repair of an AAA at our department. All patients admitted to our service were seen preoperatively by a cardiologist. Clinical evidence of angina resulted in immediate coronary angiography. Any patient with a prior history of myocardial infarction or an abnormal electrocardiogram underwent a thallium stress test. If the test results were positive, the patient underwent coronary angiography. Seventeen patients underwent combined operations. There were 15 men and 2 women. Fourteen patients had elective repair of AAA and were found to have surgical coronary artery disease at catheterization. Three patients had increasing angina and an AAA was diagnosed preoperatively. The average aneurysm size was 6.8 cm. The average age of our patients was 66 years, and the average number of bypass grafts performed concomitantly was 2.7. One patient underwent a redo coronary artery bypass.

All patients underwent a median sternotomy and cardiopulmonary bypass with myocardial revascularization before the incision was extended for an abdominal approach with subsequent aneurysm repair. Before abdominal exploration was commenced, all patients were deemed hemodynamically stable with excellent left ventricular contractility, good cardiac output, and low pulmonary artery pressure. Initial protamine infusion was calculated at one half the total dose of heparin. Atrial and aortic cannulas were removed before abdominal aortic aneurysm repair. All patients underwent an end-to-end AAA repair using the graft inclusion technique described by Javid and associates [7]. All aneurysms were infrarenal. One patient required an 8-mm graft extension to the left femoral artery because of severe iliac artery obstruction. The average cross-clamp time for the AAA repair was 38 minutes. The remaining calculated dose of protamine was given after graft placement.

Results

All patients underwent an uneventful operation. The complications after operation were as follows: One patient was returned for mediastinal bleeding. One patient underwent both mediastinal and abdominal exploration for bleeding. Both patients were extubated the next day and had an uneventful recovery. In 1 patient a tension pneumothorax developed before extubation, which responded to chest tube placement. One patient suffered a small subendocardial perioperative myocardial infarction with no serious sequelae. The overall 30-day mortality in this series was 5.9% (one death). The remaining 16 patients are alive and well at current follow-up.

Transfusion requirements averaged 4 units of packed red blood cells and 1.7 units of fresh frozen plasma for the entire series. However, after routine use of the Cell Saver

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only a total of 2 units of packed red blood cells and 2 units of fresh frozen plasma were necessary for our last 6 patients.

Comment

The combination of modern surgical technique, improved anesthetic management, and sophisticated monitoring has undoubtedly contributed to a decline in the operative mortality associated with AAA repair. In 1969, Young and co-workers [8] reported a 15% operative mortality for elective aneurysm repair. The same group decreased the operative mortality to 6% in a report in 1977. Crawford and associates [9] have reported a 1.43% operative mortality rate in their most recent series of 368 patients undergoing AAA repair. Diehl and colleagues [10] reported a 5.1% mortality rate for repair of intact AAA. Myocardial infarction was the major cause of death. Several risk factors significantly influenced postoperative mortality, including age greater than 60 years, suspected coronary artery disease, serum creatinine level greater than 180 μmol/L (2.0 mg/dL), complementary renal artery revascularization, and aneurysm rupture [11].

Although the hazards associated with repair of intact AAA have diminished within the last decade, most recent reports document a persistent operative mortality of 3% to 9%. Coronary artery disease, by a wide margin, is the leading cause of both early and late death after peripheral vascular reconstruction. Previous reports from several centers indicate that myocardial infarction is responsible for approximately half of all postoperative deaths occurring after AAA resection and extracranial or lower extremity revascularization and occur with a predictable frequency [12, 13].

Hertzer and associates [2, 11] demonstrated in 1983 with routine angiography that 31% of patients with AAA had severe correctable coronary artery disease. Almost half (44%) of the patients with a suspicious clinical history had severe coronary artery disease, whereas as many as 18% of patients with no clinical evidence of coronary artery disease had serious coronary disease.

Late survival after aneurysm repair also seems to be directly influenced by coronary artery disease. Hollier and co-workers [4] have demonstrated a 5-year survival of 67% and a 10-year survival of 40.7% in a recent series of aneurysm repairs. Late deaths were attributable to cardiac disease in 38% of patients. For patients without preoperative (pre–AAA repair) evidence of heart disease or hypertension, the 5-year mortality rate from myocardial infarction was 3.7%, compared with 11.7% for those with a positive history of hypertension and heart disease.

Whittemore and associates [14], using a Swan-Ganz catheter for optimal perioperative management, were able to achieve a 1% mortality in 110 consecutive patients requiring AAA repair. Despite this isolated study, most surgeons would agree that patients with aortoocclusive disease or AAA who require operation and also have signs and symptoms of coronary disease should undergo cardiac catheterization. Patients with serious coronary disease needing aortic aneurysm resection could undergo either a staged repair or a combined operation.

Hertzer and colleagues [15] reported in 1987 a total of 56 patients with staged AAA repair after coronary bypass, usually during the same hospital admission, with a single death (1.8%) caused by cerebral infarction. The cumulative 5-year survival rate was 75% and cardiac mortality, 5.7% after coronary bypass in comparison with a subset of patients with severe uncorrected coronary involvement with a cumulative survival of 29% and a mortality of 34%. This supports the conclusion that select patients who require elective resection of AAA also warrant myocardial revascularization in order to decrease perioperative risk and improve late survival.

Ruby and associates [16] used a selective approach in 227 patients. Two hundred seventeen patients with stable or no evidence of coronary disease were managed by standard intraoperative anesthetic management. Four patients with asymptomatic AAA underwent urgent coronary artery bypass grafting for unstable angina followed by later AAA repair. Six patients underwent a combined procedure for unstable angina and symptomatic AAA. However, 10 (13%) of those patients with "stable angina" undergoing only AAA repair had a myocardial infarction, with one cardiac-related death.

We reserve staged repair for patients with moderate to severe myocardial dysfunction requiring extensive myocardial revascularization or valve replacement. We recommend a combined operation for patients with an AAA and serious coronary artery disease. This combined approach is possible with low mortality and morbidity rates, at less cost and with decreased hospitalization.

It is not always possible to accurately predict those patients who will be at highest risk for a myocardial infarction during an AAA repair. Clinical factors predictive of risk of cardiac death in the perioperative and late postoperative period, identified in a number of studies, include: age at operation; history of heart failure, angina pectoris, or myocardial infarction; abnormal resting electrocardiogram; history of stroke; other vascular disease; previous vascular operation; hypertension; and diabetes mellitus. A multivariate analysis of cardiac risk factors in patients undergoing AAA repair showed many patients with a low computed risk will experience cardiac complications. Although coronary angiography has been advocated in all patients with peripheral vascular disease before operation, we prefer a selective approach to this problem. Patients in our institution with no evidence of coronary artery disease undergo AAA repair with intense perioperative monitoring with Swan-Ganz catheterization. Patients with angina, known coronary artery disease, or a history of myocardial infarction undergo coronary angiography. Patients with equivocal clinical findings are reevaluated by exercise stress isotope ventriculography and have coronary angiography if these results are positive.

We conclude that patients with serious coronary artery disease and AAA can safely undergo a combined procedure. The use of the Cell Saver has contributed to decreasing the need for autologous blood replacement therapy, especially in combined cardiac and vascular procedures.

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Strut Fixation of an Extensive Flail Chest

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The indications for and preferred approaches to operative stabilization of posttraumatic chest wall instability are uncertain. We suggest this simple, rapid, and effective approach to surgical stabilization by Luque rod strutting of the flail segment when operation is required.

(Ann Thorac Surg 1991;51:473–5)

The management of flail chest has been the subject of controversy for many years [1]. An individualized treatment approach focusing on the patient's posttraumatic cardiopulmonary status and the extent of trauma to other organ systems is generally supported [2]. A small number of patients who require surgical exploration to manage intrathoracic pathology or who have collapsed chests leading to pulmonary restriction may be treated best with simultaneous operative fixation of the unstable chest wall [3–5]. We present a rapid, simple technique that provides rigid support of the unstable chest wall when thoracotomy is required.

A 78-year-old man with chronic obstructive pulmonary disease fell onto his back from a 3-m height. At initial evaluation, he was noted to be in obvious respiratory distress. The patient was endotracheally intubated and placed on assisted mechanical ventilation. Physical examination showed paradoxical movement of the right lateral chest wall with spontaneous ventilation. A portable chest roentgenogram demonstrated numerous segmental fractures of the right second through tenth ribs posterolaterally. A moderate right pulmonary contusion and a pronounced hemopneumothorax was also present. A tube thoracotostomy was performed with 300 mL of blood retrieved from the chest. No other injuries were identified. An intermittent air leak present at tube insertion sealed 72 hours after injury. Chest tube drainage was minimal. Serial chest radiographs demonstrated progressive collapse of the right hemithorax, which was confirmed by computed chest tomography (Fig 1). Recurrent episodes of total atelectasis of the right lung required repeated bronchoscopic clearance of secretions. There was no endoscopic evidence of foreign body or occult bronchial tear.

Surgical chest wall stabilization was believed necessary after 3 weeks of continued ventilatory support. The chest was entered through a standard posterolateral thoracotomy. Elevation of the comminuted ribs and the collapsed chest wall facilitated decortication and reexpansion of the lung. Three 4.8-mm-diameter stainless steel Luque rods (length, 60 cm) were bent to approximate the normal internal contour of the right hemithorax. The rods were passed through the anterior chest wall above the second rib and then exited out of the posterolateral aspect of the chest over the intact 11th rib [5]. These Luque rod arches were positioned beneath the unstable chest wall segment and locked together with orthopedic external fixation devices (Fig 2). The chest was closed and drained with two 32F chest tubes. The rod struts reestablished the normal volume of the hemithorax, and the external fixation devices maintained proper rod position without migration. Weaning from the ventilator was successful over the next 4 days without further pulmonary complications. The apparatus was removed at the patient's bedside 7 weeks after its insertion with the aid of mild sedation (Fig 3). The patient's rehabilitation has progressed to independence at home with minimal support (Fig 4).

Comment

Identifying patients who require operative stabilization of the flail or unstable chest wall is difficult [4]. Many patients can be managed with careful attention to pulmonary hygiene, pain control, and cautious fluid replacement [2, 6]. Patients suffering from large flail injuries associated with a severe pulmonary contusion and pa-

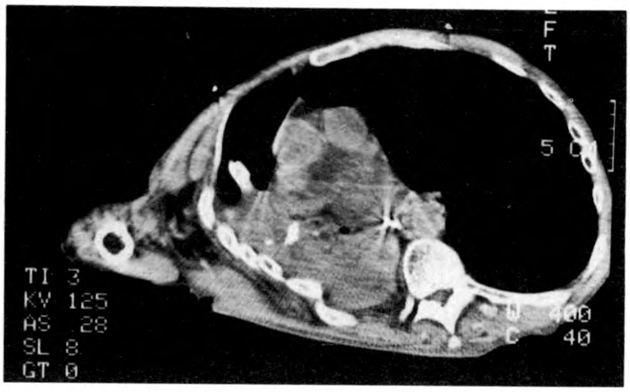

Fig 1. Computed tomogram of the chest demonstrating the loss of volume of the right hemithorax, intrathoracic rib fragments, and the associated pleural rind around the lung.

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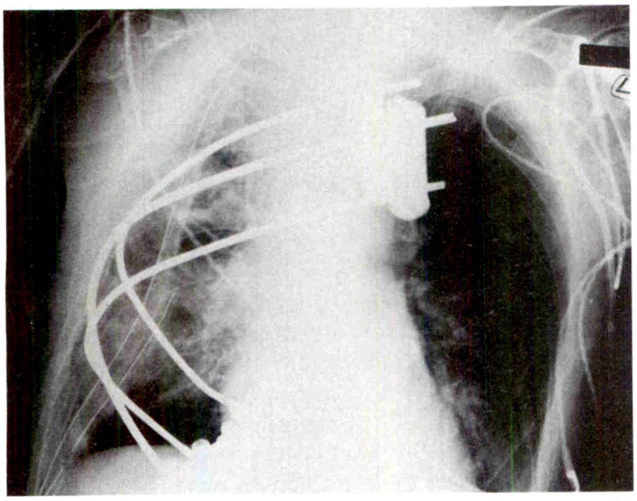


Fig 2. Luque rod fixation of the posterolateral flail chest stabilized with use of orthopedic external fixation devices.

tients with preexisting pulmonary disease may require pneumatic "internal splinting" of the injury with mechanical ventilation [7]. Endotracheal splinting of the airway is not always successful in preserving chest cage dimensions and in stabilizing the flail segment. Thomas and colleagues [3] and Moore [4] have independently observed posterior and lateral flail injuries to be particularly prone to failure with use of ventilatory support alone. They noted that progressive chest wall collapse leading to prolonged ventilatory insufficiency is common, perhaps as a result of the body's weight being constantly applied against the unstable chest wall. Even when nonoperative therapy is successful in managing the initial injury, chronic pulmonary disability related to the thoracic cage deformity is common [1]. Furthermore, the prolonged need for ventilatory support gives rise to an increased frequency of nosocomial infections and endotracheal tube–related problems [2–6].

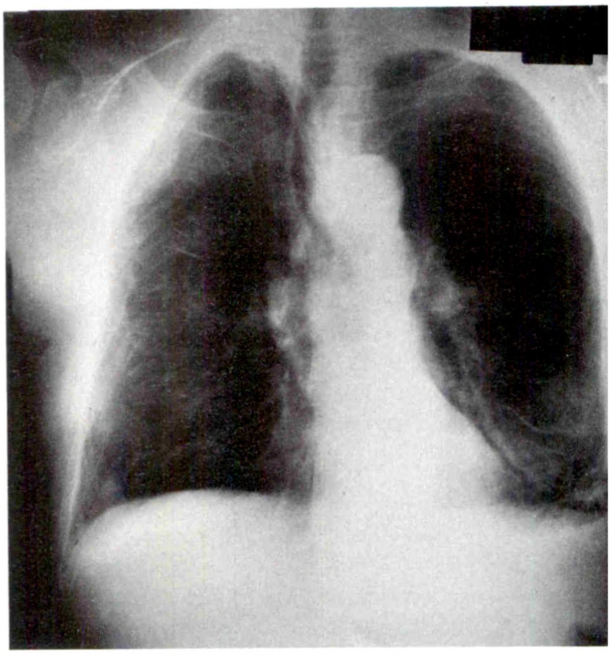
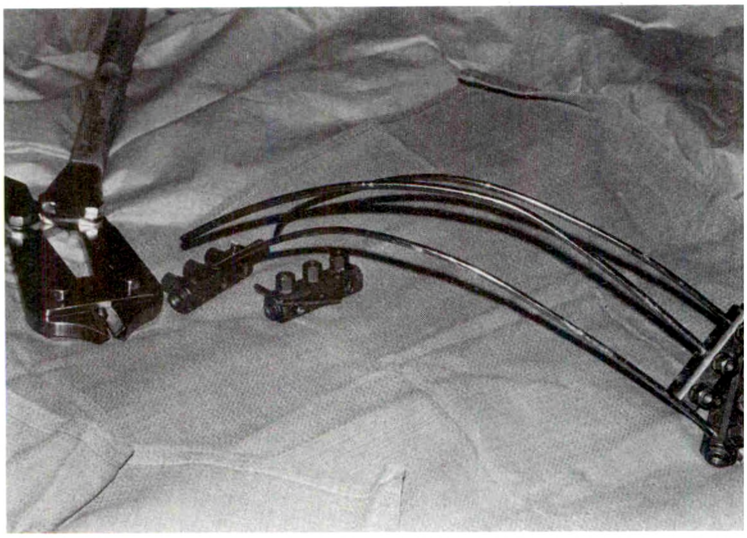


Fig 4. Chest radiograph 3 months after the removal of the stabilization device.

Several authors support early operative stabilization
posterior and lateral chest cage injuries [3–5]. This str
egy is further suggested when underlying pulmona
parenchymal or pleural pathology requires surgical atte
tion.

A variety of surgical approaches have been used in t
past, such as external towel clip traction, application
overlapping rib struts, and intramedullary wiring of t
fractured ribs [3, 5, 8]. These techniques can be difficu
time-consuming, and unnecessarily restrictive to patie
mobility. The additional dissection required to accompli
these repairs may increase local tissue injury, and i
planted foreign bodies can contribute to chronic osseo
and soft tissue infections.

Fig 3. Luque rod-orthopedic external fixation apparatus after its removal at the bedside.



The rod fixation initially described by Beltrami [5] is a rapid, simple means of accomplishing chest wall stabilization. Rod migration seen with this technique can be overcome with additional rigid external orthopedic fixation.

Operative stabilization of extensive posterior and lateral flail chest injuries should be considered when progressive collapse of the hemithorax occurs and when ventilatory failure persists long after resolution of associated pulmonary contusions. The strut fixation technique described is a simple method of chest wall stabilization for patients with these chest wall injuries.

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Left Ventricular Pseudoaneurysm With Hemoptysis

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A 53-year-old man who had previously undergone resection of a left ventricular aneurysm was admitted because of hemoptysis. Preoperative evaluation with computed tomographic scan and cardiac catheterization demonstrated a pseudoaneurysm of the inferior ventricular wall measuring 16 cm in diameter with protrusion into the left hemithorax. The neck of the pseudoaneurysm was a defect in the ventricular wall extending from the base of the mitral valve annulus to the insertion of the posterior papillary muscle. Operative repair was performed using an albumin-coated, low-porosity Dacron patch.

(Ann Thorac Surg 1991;51:476–8)

A common sequela of acute transmural myocardial infarction is the formation of a left ventricular aneurysm. Less often, a pseudoaneurysm may develop as a consequence of ventricular rupture when the hematoma is contained and organizes into a fibrous cavity. Pseudoaneurysms are found most often after inferior wall infarcts and have a propensity to rupture, even in the chronic stage [1]. Successful surgical repair, with or without concomitant coronary artery bypass, has been effective for the treatment of congestive heart failure, intractable angina, ventricular arrhythmias, and embolization [2, 3]. Recurrence of either true or false aneurysm after repair has been an infrequently documented complication [4]. This report describes a patient in whom a left ventricular pseudoaneurysm developed that was seen with hemoptysis 21 months after primary repair.

A 51-year-old man suffered an acute inferior wall infarction in April 1988. Ten days later, he underwent cardiac catheterization and was found to have a total occlusion of the mid-right coronary artery, normal left-sided coronary anatomy, and an akinetic inferior wall on ventriculogram. He was treated medically, remained stable, and was discharged. Seven weeks later, he was rehospitalized for symptoms of congestive heart failure. Chest roentgenogram on admission showed a markedly enlarged cardiac silhouette, and a computed tomographic scan of the chest showed a large aneurysm of the inferior ventricular wall.

At operation, the aneurysm measured 15 × 10 cm and required opening of the pericardium into the left chest to gain full exposure. The defect extended up to the base of the mitral valve but without impairment of the valve mechanism.

An aneurysmectomy was performed, and a primary repair was completed with approximation of the edges using two strips of Teflon felt. The patient did well for 10 months before he began to experience recurrent symptoms of mild congestive heart failure and a persistent, dry cough. These symptoms continued for the next 11 months without worsening until hemoptysis developed. He was seen at his local emergency room where it was estimated that he had coughed up 300 to 400 mL of blood.

He was transferred to Deborah Heart and Lung Center on March 23, 1990, where an ultra-fast cine computed tomographic scan was performed, and this showed a 16 × 10-cm pseudoaneurysm in the area of previous repair with extension into the left hemithorax (Fig 1). There was abutment of the left lower lobe with atelectasis from the compression. Cardiac catheterization demonstrated the inferior wall defect with filling of the pseudoaneurysm cavity (Fig 2). There had been no progression of coronary disease, and there was no evidence of mitral regurgitation. The operative repair was undertaken with exposure of the common femoral vessels but without heparinization or cannulation before resternotomy. The dissection was accomplished such that the ascending aorta and right atrium were cannulated in routine fashion, and the remainder of the procedure was performed with standard cardiopulmonary bypass techniques. The pseudoaneurysm was not completely freed from the adjacent left lung; but with the heart arrested, the pseudoaneurysm was opened and found to be partially filled with clot. Removal of the clot allowed full exposure of an 8-cm elliptical defect in the true ventricular wall. Interrupted 0-Polydek (Deknatel, Fall River, MA) sutures with pledgets were placed circumferentially around this fibrous ring and an albumin-coated, low-porosity Dacron patch (C.R. Bard, Inc, Billerica, MA) was then placed to close the defect. This suture line was then oversewn with a running 2-0 monofilament suture. The patient was weaned from cardiopulmonary bypass without difficulty on low-dose dopamine.

The postoperative course was unremarkable, and the patient was discharged on the 12th postoperative day. A

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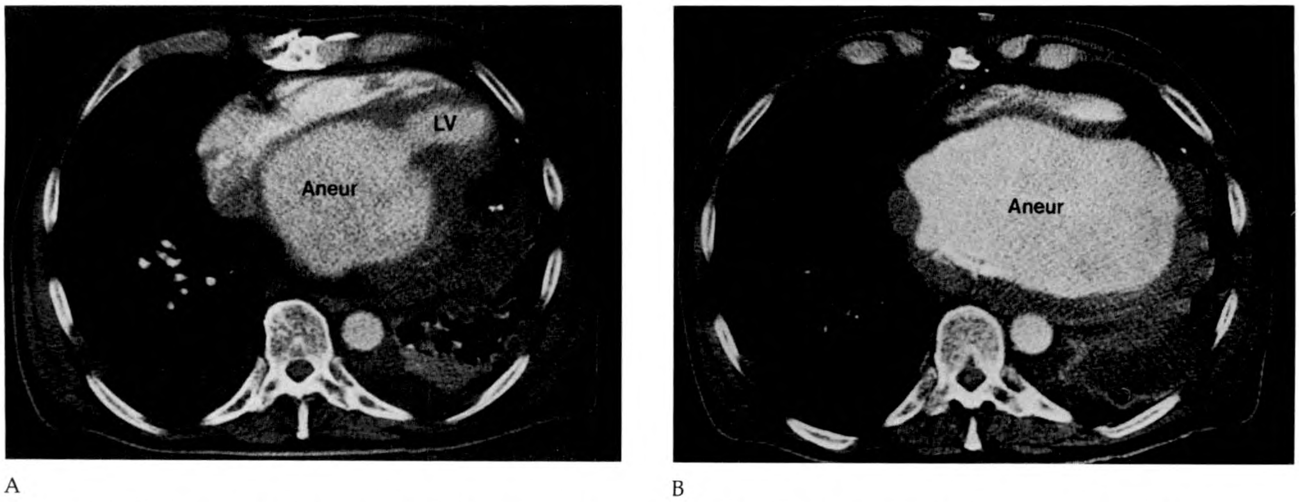

Fig 1. Preoperative computed tomographic scan with cuts showing ventricular wall defect and extension of pseudoaneurysm inferiorly and laterally into the left hemithorax. (Aneur = *pseudoaneurysm;* LV = *left ventricle.)*

follow-up computed tomographic scan was obtained showing a satisfactory repair (Fig 3).

Comment

Left ventricular pseudoaneurysm formation is a rarely reported complication after primary plication or aneurysmectomy. Most likely, these patients die suddenly from rupture without the opportunity for diagnostic evaluation. In contrast to true aneurysms, which possess a scarred transmural myocardium, the pseudoaneurysm is devoid of myocardial scar tissue and has only a thin-walled fibrotic capsule. Thus, it is more prone to rupture spontaneously even in its chronic stage [1].

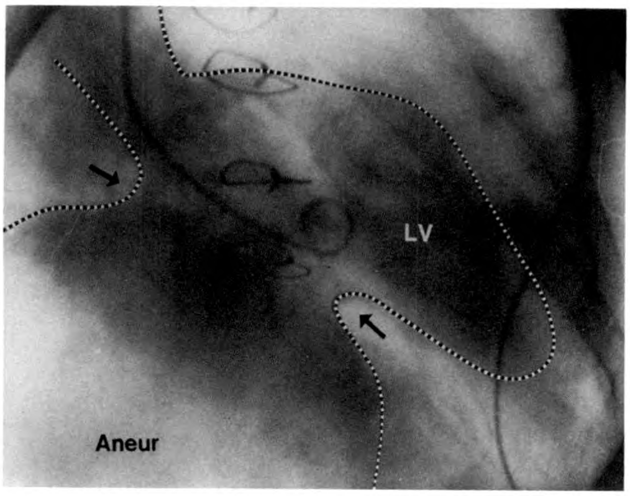

Fig 2. Ventriculogram with contrast outlining the neck of the defect (arrows) *and filling the pseudoaneurysm* (aneur) *cavity.* (LV = *left ventricle.)*

The patient in this case was fortunate enough to have had a "herald bleed" that prompted him to seek medical attention. This hemoptysis was an ominous sign of impending rupture. His symptoms over the previous few months of mild congestive heart failure and chronic cough were indicative of expansion of the pseudoaneurysm and impingement upon the left lung. The hemoptysis signaled the final erosion into the bronchial tree. Normally, the pericardium would contain any rupture within the pericardial space and lead to hemopericardium, tamponade, and eventual death in a short period of time unless there was immediate surgical intervention. However, because the pericardium in this case was opened into the left chest at the initial operation, there was no restrictive barrier to erosion into the lung.

Two previous case reports have documented pseudoaneurysmal erosion into the lung with development of a ventriculopulmonary fistula [5, 6]. In both reports, an infectious process was believed to be the cause of the dehiscence. Teflon felt strips used to buttress the repairs were implicated as the nidus of infection. This patient was different in that no infection was identified intraoperatively or by culture of the Teflon felt strips. Most likely, the attempt to primarily close a large defect eventually led to its breakdown.

This case is of interest in that the patient was examined because of hemoptysis and was able to undergo evaluation and repair before exsanguination occurred. This report suggests that a recurrent pseudoaneurysm should be treated with the same surgical urgency as a primary pseudoaneurysm because of the propensity to rupture. The operative approach should limit dissection of adjacent tissues, obtaining only enough exposure to enter the false aneurysm such that the repair can be carried out from within the cavity. Also, to prevent recurrent pseudoaneurysm formation, consideration should be given to the use of a patch instead of primary repair to

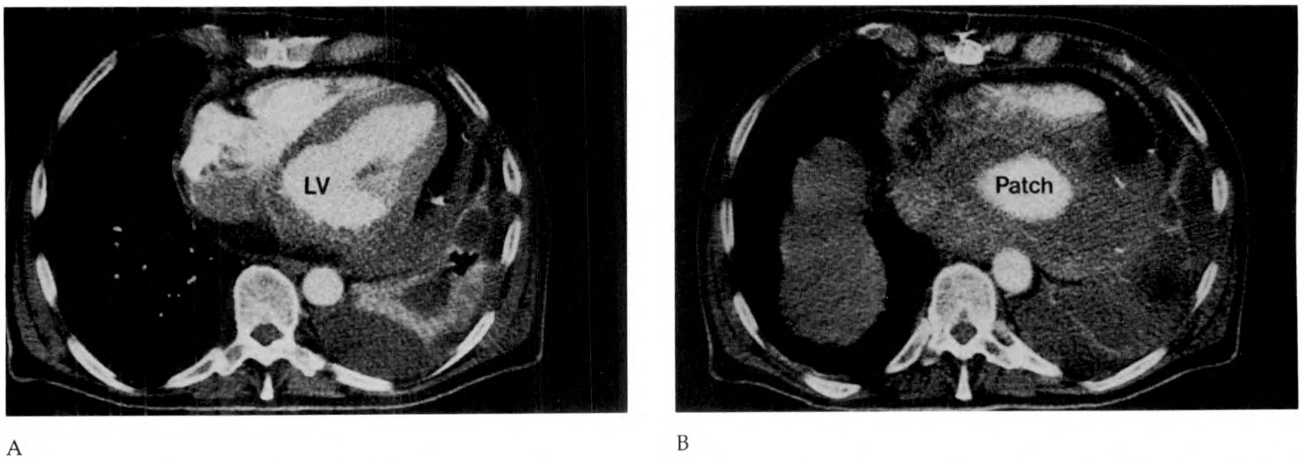

Fig 3. Postoperative computed tomographic scan with cuts at approximately the same level as the preoperative scan, showing satisfactory repair. (LV = *left ventricle;* Patch = *inferior extent of Dacron patch.)*

avoid undue tension on the suture line when the aneurysm is found on the inferior left ventricular wall.

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An Unusual Complication of Cardiac Transplantation—Infected Aortic Pseudoaneurysm

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Infections after cardiac transplantation are a frequent cause of early morbidity and mortality. An unusual site for such a complication is at the aortic anastomotic suture line. We report a case of an infected aortic pseudoaneurysm, seen as recurrent septicemia, during the first 6 months after cardiac transplantation.

(Ann Thorac Surg 1991;51:479–81)

Infected pseudoaneurysms may arise after reconstructive arterial operations. Reports of this complication occurring after renal transplantation have appeared [1–3]. In this report, we describe a patient who was admitted to our hospital 5 months after cardiac transplantation with a puzzling history that included three episodes of meningitis and two episodes of bacteremia caused by *Pseudomonas aeruginosa*.

A 39-year-old man who had undergone cardiac transplantation 5 months earlier at another hospital was admitted to the Portland VA Medical Center with a 1-day history of severe headache, lethargy, neck pain, fever, photophobia, nausea, and vomiting. Two separate sets of blood cultures were positive for *P aeruginosa*, but the initial clinical evaluation failed to identify the origin of the septicemia. In particular, a computed tomographic scan of the head demonstrated no change from previous examinations. Although a lumbar puncture yielded cloudy cerebrospinal fluid with its cell counts and chemistry consistent with a low-grade meningitis, cultures were sterile. The patient responded to therapy with tobramycin and ceftazidime, becoming afebrile and asymptomatic on the third hospital day. He eventually received a 6-week course of these antibiotics.

Review of the patient's medical records from the transplantation center showed a complicated postoperative course. The major events included several episodes of atrial fibrillation, an episode of acute rejection, a 4-day episode of bacteremia caused by *P aeruginosa*, two strokes, multifocal infarction of the terminal ileum, and two febrile episodes associated with low-grade meningitis. The meningitis episodes occurred when the patient had been off antibiotics for several days but cerebrospinal fluid and blood cultures were sterile. The patient received three courses of parenteral antibiotics totaling 57 days for his bacteremia and two bouts of meningitis. On each occasion, he had defervescence and became asymptomatic within a few days. Of note, the origin of the pseudomonas bacteremia was never established with certainty though a urine culture was positive during the episode. Immunosuppressive therapy was initiated after transplantation and was maintained throughout this period with prednisone, azathioprine, and cyclosporine. At no time was the patient neutropenic. Additionally, one episode of acute rejection was treated with a 1-g intravenous dose of methylprednisolone 16 days after transplantation—13 days before his bacteremia ensued. Repeated performance of endomyocardial biopsies during his remaining hospitalization did not show any further episodes of rejection.

At our hospital, the patient underwent a number of diagnostic tests in an effort to locate the source of his recurrent pseudomonas bacteremia. Ultimately, a chest computed tomographic scan with contrast medium (Fig 1) disclosed a large vascular mass in the anterior mediastinum. A magnetic resonance imaging scan (Fig 2) and an angiogram of the aortic root (Fig 3) confirmed this abnormality and identified a large, approximately 8 × 8 cm, pseudoaneurysm of the ascending aorta.

After these tests, the patient was taken to the operating room for excision of the large pseudoaneurysm and for repair of the ascending aorta. Cardiopulmonary bypass was instituted through femoral artery cannulation and right atrial drainage. The patient was cooled to 26°C with minimal dissection of the aortic root to reduce the risk of emboli. The aorta was clamped high at the level of the innominate artery before any manipulation of the pseudoaneurysm. The pseudoaneurysm was opened through to normal aorta, approximately 1 cm above the aortic commissures, and cold blood cardioplegia was injected directly into the coronary ostia. Dissection of the ascending aorta, pseudoaneurysm, and mediastinal tissues made resection possible, and an end-to-end anastomosis was completed with 4-0 Prolene suture (Ethicon, Somerville, NJ), without the use of any prosthetic graft material. Histological examination of the resected aneurysm demonstrated some inflammatory cells in the necrotic material and clot filling the aneurysm, but Gram stains and cultures of this material were negative.

The patient did well postoperatively but died 8 months

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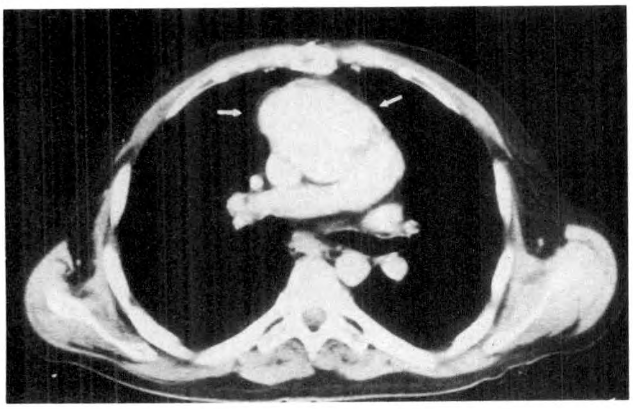

Fig 1. Computed tomographic scan with contrast enhancement shows posterior displacement of the ascending aorta by a late enhancing aortic pseudoaneurysm (arrows).

later of an episode of acute rejection. During this period, he exhibited no manifestations of ongoing infection at the operative site. At autopsy, the aortic repair site was found to be intact with no evidence of inflammation or infection.

Comment

Infectious complications after cardiac transplantation are major causes of both early and late mortality and morbidity [4–6]. We report here an infected pseudoaneurysm at the suture line of the ascending aorta where the donor aorta was joined to the recipient's aorta.

Arterial lesions of this type are thought to develop in patients with endocarditis from septic emboli lodging in the vasa vasorum of afflicted vessels. In other settings, they develop from an extension of a contiguous focus of infection or from direct implantation at the time of arterial injury. It seems more likely that our patient's infection developed from hematogenous seeding of damaged intima during the course of a bacteremia originating at another site. The arterial injury resulting from the creation of the aortic anastomosis in combination with foreign bodies, ie, buttressing pledgets and suture material, acted as a nidus for infection during a bacteremia, which may have originated in the urinary tract in association with perioperative urethral catheterization. The positive urine culture for *P aeruginosa* at the time of the initial bacteremia offers some support for this contention.

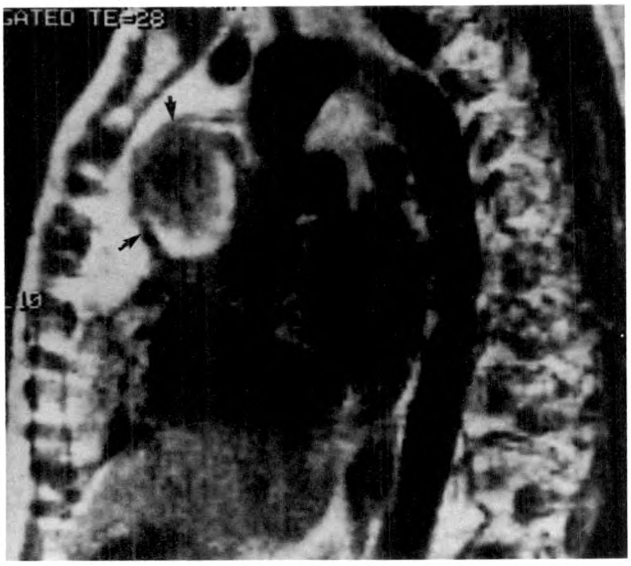

Fig 2. Sagittal magnetic resonance imaging scan (gated ecno time = 28 ms) shows high signal mass in retrosternal region with the signal from ascending aorta being displaced posteriorly (arrows).

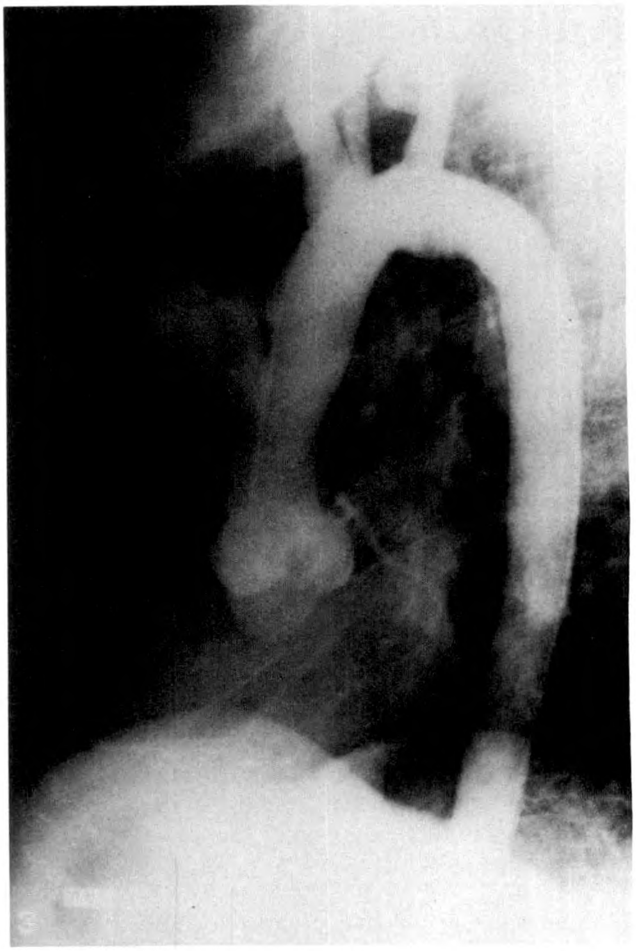

Fig 3. Thoracic aortogram in the right posterior oblique projection. Aortic root and coronary arteries are normal. Pseudoaneurysm with wide neck is well seen.

Our patient demonstrated several important clinical features of an infected aneurysm: persistent and recurrent bacteremia and embolic phenomena. The aneurysm was easily detected by two noninvasive imaging techniques used: computed tomography of the chest with contrast enhancement (Fig 1) and magnetic resonance imaging (Fig 2). Either procedure would suffice as a screening test for this condition in a high-risk patient. In our patient, arteriography (Fig 3) helped in planning the surgical approach. Echocardiography was not helpful in diagnosing our patient's aneurysm because the anastomotic site on the aorta was too high to be visualized.

The treatment of infected aneurysms usually combines surgical resection and arterial reconstruction or vascular bypass with a prolonged course of parenteral antibiotic therapy. This course of action was chosen in this patient, and the results were gratifying. This is especially noteworthy in view of the etiological agent, *P aeruginosa*. The futility of antibiotic therapy alone was well illustrated in our patient's course of recurrent sepsis and its complications.

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Procainamide-Induced Respiratory Insufficiency After Cardiopulmonary Bypass

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A 46-year-old man could not be weaned from ventilatory support while receiving procainamide. When the drug was discontinued, the patient was successfully weaned shortly thereafter.

(Ann Thorac Surg 1991;51:482–3)

Procainamide is used commonly after cardiopulmonary bypass in the treatment of a wide variety of cardiac arrhythmias. Well-recognized adverse effects of the drug include hypotension, gastrointestinal symptoms, fever, agranulocytosis, and a systemic lupus erythematosus–like syndrome. An infrequent but potentially lethal side effect is the ability of procainamide to induce a myasthenia gravis–like syndrome with associated muscle weakness [1, 2]. If unrecognized, the syndrome can result in an inability to wean a patient from the ventilator. The purpose of this report is to call attention to the potential hazard of procainamide in producing muscle weakness and associated respiratory insufficiency.

A 46-year-old man underwent a second triple aortocoronary bypass graft. Despite marked impairment of ventricular function (ejection fraction, 0.18) preoperatively, he was weaned from cardiopulmonary bypass with 3 μg/kg of dobutamine. His immediate postoperative course was uncomplicated, and his inotropic support was discontinued on the first postoperative day. He was weaned from ventilatory support and was extubated the morning after his operation. However, on the third postoperative day, recurrent supraventricular and ventricular arrhythmias developed, requiring multiple electrocardioversions, reintubation, and mechanical ventilatory support. Because of recurrent arrhythmias, he was begun on a regimen of intravenous procainamide and amiodarone. This regimen was successful in preventing further arrhythmias. He was receiving 500 mg of Procan SR (procainamide hydrochloride) four times daily through a nasogastric tube. The NAPA and Procan were always in therapeutic range. However, despite a clear chest roentgenogram and no fluoroscopic evidence of phrenic nerve palsy, we were unable to wean the patient from the ventilator. Therefore, a tracheostomy was performed 3 weeks later. Because there was the possibility of procainamide-induced muscular weakness, the procainamide therapy was discontinued. He was on no other medications that could cause muscular weakness.

Shortly thereafter, the patient began tolerating progressively longer periods of time without ventilatory support and was successfully weaned from the ventilator 10 days after cessation of procainamide. The long period required for complete weaning from the ventilator was secondary to his preoperative cachectic status. Although postoperatively pulmonary symptoms never developed, he did undergo orthotopic cardiac transplantation 2 years postoperatively because of recurrent congestive heart failure and angina. He was extubated on the day after transplantation.

Comment

Procainamide is an effective antiarrhythmic agent and has been used frequently after cardiopulmonary bypass for the treatment of supraventricular and ventricular arrhythmias. In recent years, several authors have demonstrated that the administration of procainamide may be associated with progressive weakness of the extraocular, bulbar, and skeletal muscles [3–5]. Nikan and associates [3] described a patient with uremic peripheral neuropathy in whom intermittent weakness of bulbar, extraocular, and skeletal muscles developed while he was receiving procainamide. In that patient, procainamide was unquestionably responsible for the myastheniallike syndrome, as all clinical and electrical manifestations disappeared after discontinuation of the drug. As occurred in our patient, skeletal muscular weakness can develop without bulbar or ocular weakness.

Drachman and Skom [4] chronicled in detail the increased muscular weakness that occurred in a patient with myasthenia gravis in whom procainamide was administered to control a cardiac arrhythmia. On the basis of their study, they cautioned against the use of procainamide in patients with myasthenia gravis.

The precise mechanism by which procainamide interferes with neuromuscular transmission has been studied, and it appears that there are three ways in which it acts at the myoneural junction: by interfering with the formation or release of acetylcholine, by antagonizing the depolarizing effect of acetylcholine, and by increasing the stability of the muscle membrane to ionic flux.

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Exacerbation of muscular weakness in patients with and without myasthenia gravis appears to occur in association with administration of short duration (less than 2 weeks). This was the situation with our patient, who received the drug only in the postoperative period. The possibility that this represented a case of autoimmune myasthenia gravis unmasked by procainamide must be considered. The marked improvement in this patient's ventilatory status on discontinuation of the drug, the fact that he was extubated immediately after transplantation, the lack of an increase in acetylcholine receptor antibodies, and the lack of response to anticholinesterase drug make that possibility highly unlikely.

Although procainamide-induced muscle weakness is an uncommon occurrence in patients without myasthenia gravis, this complication must be considered in those patients in whom respiratory insufficiency develops while they are receiving this drug.

We wish to thank Mr Louis Buckberg for his invaluable suggestions in the management of this patient.

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Repair of Posterior Left Ventricular Aneurysm in a Six-Year-Old Boy

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Left ventricular aneurysms and diverticula are rarely encountered in the pediatric age group. This paper reports a case of congestive heart failure and mitral regurgitation in a 6-year-old boy with a large posterolateral left ventricular aneurysm. Complete repair was successfully performed by excision of the aneurysm and Dacron patch reconstruction of the left ventricular free wall. The patch extended onto the posterior annulus of the mitral valve, thus restoring the mitral valve to normal geometry and correcting the mitral insufficiency. The surgical literature on congenital cardiac diverticula and acquired aneurysms in children is reviewed and summarized.

(Ann Thorac Surg 1991;51:484–7)

True ventricular aneurysms in children, as in adults, are acquired and have been associated with trauma [1–3], vasculitis or myocarditis [4, 5], congenital tissue weakness [6], cardiac operation [7], anomalous origin of the left coronary artery [8, 9], and, more frequently, with unknown causes [10].

This report is on a rare case of true ventricular aneurysm of unknown cause in a 6-year-old boy and on a review of the English-language literature on successful open repair of left ventricular (LV) aneurysms in children.

A 6-year-old boy from the Dominican Republic was admitted to NYU/Bellevue for evaluation and possible resection of an LV mass. One year before admission, he was seen with dyspnea, dysphasia, weight loss, and fatigue. The medical history was negative for trauma or any other significant illness. A systolic murmur compatible with mitral insufficiency was noted. Congestive heart failure was diagnosed, and the patient was placed on a regimen of digoxin and diuretics. Chest roentgenogram showed considerable cardiomegaly, and computed tomographic scan of the chest showed a mass adjacent to and compressing the left ventricle. An attempt at needle aspiration of the mass was nondiagnostic, and the child's symptoms continued to worsen.

Physical examination on admission was remarkable for a right precordial bulge and a prominent precordial impulse in the right parasternal area. A grade 3/6 systolic murmur was heard at the left lower sternal border, and cardiac catheterization confirmed the presence of moderate mitral insufficiency. The chest roentgenogram on admission showed a cardiothoracic ratio of 0.77 with enlargement of the cardiac shadow to the left and posteriorly. The electrocardiogram showed right-axis deviation, biventricular hypertrophy, and a deep Q wave in V_5 and V_6. The echocardiogram confirmed by a magnetic resonance imaging scan showed a large (8 × 8 cm) aneurysm that originated from the posterolateral left ventricle free wall, appeared to communicate with the LV cavity, and was partially filled with thrombus. Fear of dislodging any of this thrombus prevented injection of contrast material into the left ventricle. Nevertheless, cardiac function was well preserved, and the LV end-diastolic pressure was normal.

The child was taken to the operating room for surgical repair of the aneurysm. The procedure was performed using moderately hypothermic (22°C) cardiopulmonary bypass. The myocardium was protected with cold blood potassium cardioplegia combined with continuous topical saline irrigation. The LV aneurysm was large, with a volume approximately twice that of the LV cavity (Fig 1). The aneurysm protruded posterolaterally, displacing the heart to the right, and was fibrous with a thick wall (9 mm). A clot with central liquefaction was present within the aneurysm mass. The edge of the aneurysm involved the mitral valve annulus and the posterior attachments of the mitral valve. A second, smaller aneurysm was found just inferior and subvalvar to the mitral apparatus. The larger posterolateral aneurysm was excised totally, leaving a defect of 2.5 cm, and the smaller inferior outpouching was obliterated from within the ventricular cavity using interrupted figure-of-8 sutures. The defect was then closed by placement of a Dacron patch using continuous 4-0 Prolene (Ethicon, Somerville, NJ) sutures. The patch extended onto the posterior annulus of the mitral valve and was placed so as to correct the preexisting deformity in the mitral apparatus. Direct closure of the ventricular free wall would have certainly resulted in worsening of the already severe distortion of the mitral valve.

Cardiac function was excellent after operation, and no pressor support was required. Likewise, the remainder of

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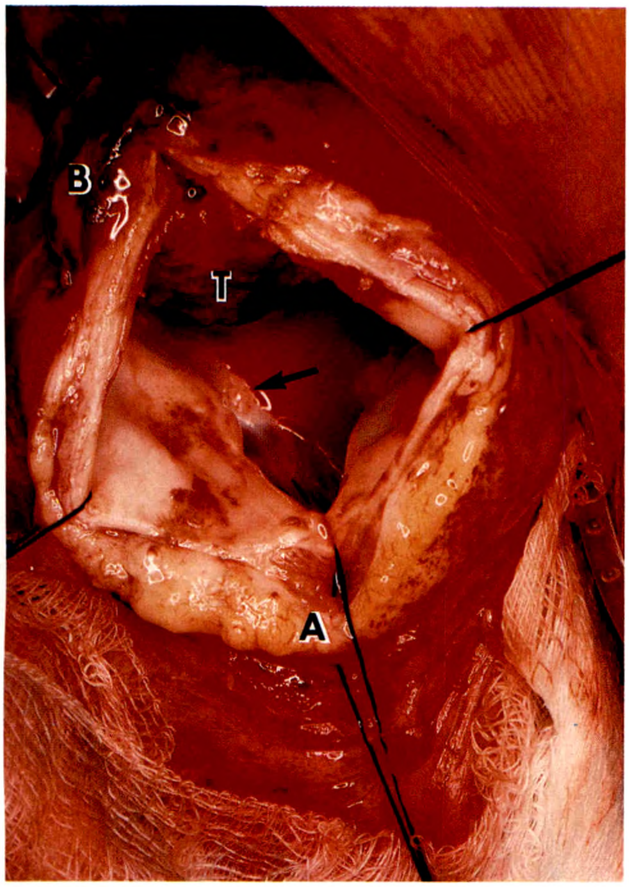

Fig 1. Gross photograph showing the aneurysm partially incised and retracted open, allowing a view from the posterolateral aspect of the left ventricle. The apex of the heart (A) *is tilted up (left), whereas just above the base of the ventricle* (B), *intracavitary thrombus* (T) *is clearly visible. The aneurysm sac continued behind the thrombus down to the annulus, encroaching upon the mitral apparatus* (arrow *points to posterior mitral leaflet).*

the postoperative course was uncomplicated. Late echocardiography confirmed the absence of residual mitral insufficiency. The child was discharged on the eighth postoperative day without cardiac medications and remains asymptomatic at 1 year after operation. Pathological review of the specimen showed dense fibrous tissue and organizing thrombus. Multiple sections failed to show any myocardial fibers.

Comment

Outpouchings of the ventricular chambers have been classified as diverticula, aneurysms, or, more rarely, epicardial cysts. Diverticula can be distinguished from true aneurysms in that diverticula have all the layers of the ventricular wall intact [11], are capable of contraction, or are associated with congenital cardiac and somatic defects [12–15]. Some have misleadingly used the term "congenital aneurysm" to denote a diverticulum. Recently, Hamaoka and colleagues [16] reviewed 18 cases of ventricular aneurysms and diverticula and attempted to maintain the distinction between aneurysms and diverticula by labeling as "aneurysms" those structures associated with evidence of acquired myocardial damage and naming structures "diverticula" when they were associated with congenital cardiac and somatic defects.

Diverticula typically arise in the apex, consist of thinned myocardium, and may contain fibrous septations [17]. It has been postulated that during cardiac development, a defect in the embryonic ventral portion of the septum transversum can lead to defects in the pericardium, diaphragm, and heart, resulting in a cardiac diverticulum [13, 18]. Apical diverticula were treated as early as 1912 by reduction into the pericardium [19], and in 1944, an apical diverticulum was resected by closed ligation [20].

Epicardial cysts are a rare condition in which sinusoids occur in the myocardium. These sinusoids may or may not directly connect to the ventricular chamber [21]. Subepicardial cysts have also been reported and are composed of ciliated columnar epithelium-lined cavities. Subepicardial cysts are probably derived from embryonic rests of bronchial tissue located in a subepicardial position [21].

Malarial infection was loosely associated with LV aneurysms in 3 autopsy cases reported from Africa [22]. An interesting subtype of LV aneurysm, the "annular subvalvular," was initially reported in an autopsy series from Nigeria [6] and was subsequently described by others [23–25]. Such an aneurysm originates just under the aortic valve or the mitral valve annuli, and although the exact cause is unknown, the defect appears to be due to an acquired weakness in the fibrous tissue adjacent to the annulus. Mitral insufficiency can occur when an aneurysm involves the mitral valve annulus, but mitral insufficiency has also been reported in association with apical aneurysms [26].

A review of the English-language literature (Table 1) showed 10 reports of successful open repair of LV aneurysms in children, although it seems likely that numerous similar repairs have not been reported. The youngest reported case of LV aneurysm repair was in a 4-month-old infant in whom the aneurysm was associated with anomalous origin of the left coronary artery [9]. All cases of symptomatic diverticula reported have been treated with closed ligation, although it appears that most authors repaired aneurysms using bypass and an open technique.

The case presented here falls into the category of a true aneurysm, probably of the annular subvalvar type. There were no associated somatic defects, and there was clear pathological evidence of myocardial obliteration within the aneurysm wall. However, the cause of this posterolateral subvalvar aneurysm was not clear. The aneurysm was subvalvar and extended onto the mitral valve apparatus, causing valvar dysfunction and regurgitation. During aneurysmectomy, the residual ventricular wall defect was of such a size that simple approximation of the edges would have distorted the posterior mitral valve annulus and further compromised valvar function. Thus, a Dacron patch was used to better restore the geometry of the ventricular free wall and the mitral apparatus. This al-

Table 1. Summary of English-Language Literature on Successful Open Repair of Left Ventricular Aneurysms in Children

Year	Author [Ref no]	Patient's Age	Cause	Location	Operation
1964	Dubb [27]	12 y	Rheumatic fever?	Apical	Open resection
1965	Davilla [18]	14 mo	Unknown	Apical	Open resection
1968	Johansson [28]	4 y	Unknown	Apical	Open resection
1974	Turina [9]	4 mo	Anomalous LCA	Anterior	Open resection ligate LCA
1975	Flemma [8]	23 mo	Anomalous LCA	Anterior bypass	Open resection
1976	Alday [29]	14 y	Congenital, subpulmonary stenosis	Septal	Open resection relieve pulmonary stenosis
1978	Wennevold [30]	9 mo	Unknown	Apical	Open resection
1981	Smith [2]	8 y	Trauma	Anterior septal	Open resection
1981	Szarnicki [31]	6 y	Unknown	Inferior	Open resection
1981	Rheuban [1]	4 y	Trauma	Posteroinferior	Open resection

LCA = Left coronary artery.

lowed correction of the mitral insufficiency at the time of aneurysm repair.

In summary, in this case a very large posterolateral LV aneurysm resulted in mitral insufficiency and congestive heart failure in a 6-year-old boy. The pathological findings exemplify the acquired nature of childhood LV aneurysms with pathological evidence of myocardial injury. Surgical repair of LV aneurysms can be successfully performed in small children, but special care should be taken to preserve the geometry of the LV wall and the adjacent valvar structures. Use of a Dacron patch for aneurysm repair is recommended when childhood aneurysms extend into close proximity with the mitral valve apparatus.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 16, 1992. The closing date for registration is August 1, 1991.

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Carcinosarcoma of the Lung With Hypertrophic Pulmonary Osteoarthropathy

CPT Paul Meade, MD, CPT John Moad, MD, MAJ Douglas Fellows, MD,
and MAJ Carl W. Adams, MD

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Carcinosarcoma of the lung is a rare malignancy. Endobronchial and parenchymal variants are classically described. Clinicopathological features are often related to anatomical location, as is the case for most lung neoplasms. This case report details the surgical management of a carcinosarcoma in a patient seen with pulmonary osteoarthropathy.

(Ann Thorac Surg 1991;51:488–90)

Carcinosarcoma is a term used to describe a group of neoplasms possessing both malignant epithelial and mesenchymal elements. Pulmonary carcinosarcoma is an exceedingly uncommon malignant tumor with less than 100 cases reported to date. The clinicopathological features of patients with this neoplasm are related to the size and anatomical location of the lesion. This report discusses an interesting presentation of hypertrophic pulmonary osteoarthropathy in a patient with carcinosarcoma, while reviewing the clinical, pathological, and surgical hallmarks of this unique tumor.

A 54-year-old man in his usual state of good health was seen with the chief complaint of bilateral lower extremity edema, with associated pain and stiffness in both knees and ankle joints that was progressive over a 3-month period. Further history related a persistent nonproductive cough of 3 years' duration with no hemoptysis and no episodes of pneumonia. The patient described dyspnea on exertion without chest pain for 6 months and had a negative cardiac history otherwise. There was a 75–pack-year smoking history. Examination was clinically significant for gynecomastia, +2 pretibial edema bilaterally, and otherwise normal cardiac and pulmonary examinations. There was no evidence of adenopathy.

Chest roentgenograms showed clear lung fields containing a 9.5-cm soft-tissue density in the superior aspect of the left lower lobe with no evidence of hilar or mediastinal adenopathy (Fig 1). Lower extremity films showed periosteal new bone formation along the distal femurs, tibias, and fibulas. Pulmonary function tests included: forced expiratory volume in 1 second, 2.41 L; forced vital capacity, 3.04 L; and a room air arterial gas of pH 7.42; carbon dioxide tension, 38 mm Hg; oxygen tension, 84 mm Hg; HCO_3, 24 mEq/L; 96% saturation.

Bronchoscopy demonstrated a normal tracheobronchial system on the right. There was mild erythema of the left main bronchus and a normal trifurcation of the left upper lobe bronchi. Two tertiary bronchioles in the superior segment of the left lower lobe were occluded by an extrinsically compressing mass. A chest computed tomographic scan documented no mediastinal adenopathy or invasion of the chest wall (Fig 2). Multiple biopsies, both bronchoscopic and computed tomographic scan–directed, were negative for malignancy. The remainder of this patient's workup included a metastatic survey, which was unrevealing. The bone scan confirmed changes of hypertrophic pulmonary osteoarthropathy noted by previous plain films. Operative resection was planned for what was believed to be an aggressive, local neoplasm or subclinical infectious process.

A left posterolateral thoracotomy demonstrated the mass to be contained within the left lower lobe. There was no involvement of the chest wall and no endobronchial component was present. The lesion was resected by formal lobectomy, and on gross section, it was an apically situated, 10.5-cm diameter, well-circumscribed, soft, tan-white tumor. The cut surface was glistening with foci of hemorrhage and central necrosis (Fig 3).

Light microscopic examination demonstrated interweaving fascicles of spindle-shaped cells surrounding epithelial glandular formations. The focal glandlike structures stained positively with keratin and epithelial membrane antigen, whereas the predominant spindle cell component did not stain. Transmission electron microscopy corroborated the biphasic nature of the tumor in demonstrating tonofiloments and desmosomes associated with the epithelial elements and a conspicuous lack of these structures within the spindle cell component. This mass represented a non–small cell tumor with both epithelial and mesenchymal differentiation consistent with a carcinosarcoma. There was no microscopic evidence of lymph node metastases making this an American Joint Cancer Committee stage I (T2 N0 M0) lesion.

The patient's postoperative course was uneventful without major complications. At the time of discharge, no further therapy was recommended.

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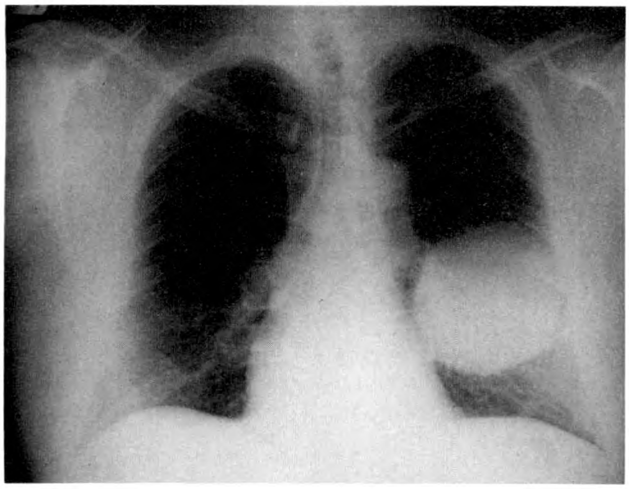

Fig 1. Chest roentgenogram demonstrating mass in the left lower lobe.

Comment

Primary pulmonary carcinosarcoma is a rare neoplasm that may be seen as a polypoid endobronchial lesion or as a peripheral parenchymal mass [1, 2]. The clinical profile of a patient with this tumor, as described in this report, is usually a man with a heavy smoking history in his sixth decade of life [3, 4]. Other common, nonspecific clinical features of this tumor cited in the majority of case reviews [1, 4, 5] include: cough, dyspnea on exertion, hemoptysis, fever, malaise, and weight loss. Localized clinical findings occur when relatively small endobronchial lesions cause an obstructive symptom complex, eg, atelectasis, bronchiectasis, pneumonia, and abscess, although considerably larger parenchymal lesions expand peripherally with eventual painful involvement of the chest wall. Thus, polypoid endobronchial lesions produce symptoms of bronchial obstruction relatively early in their course. Because of this, they offer a better prognosis after surgical resection than do the larger parenchymal lesions, which are relatively asymptomatic until late in the disease process when metastases have often occurred [1, 4–6]. As in this case, attempts to perform a biopsy on this malignancy are often unrewarding, often owing to tumor necrosis [4–6].

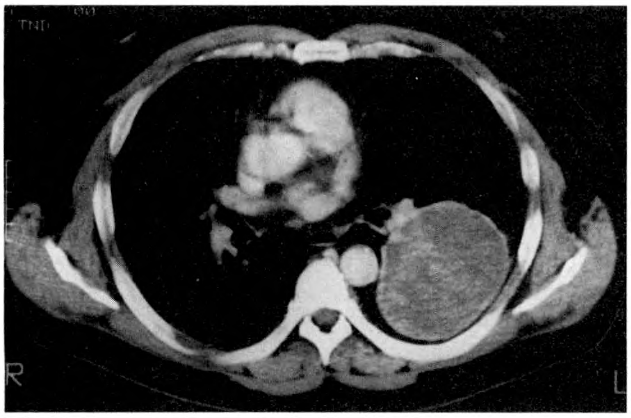

Fig 2. Computed tomographic scan demonstrating same lesion with no obvious invasion of left wall.

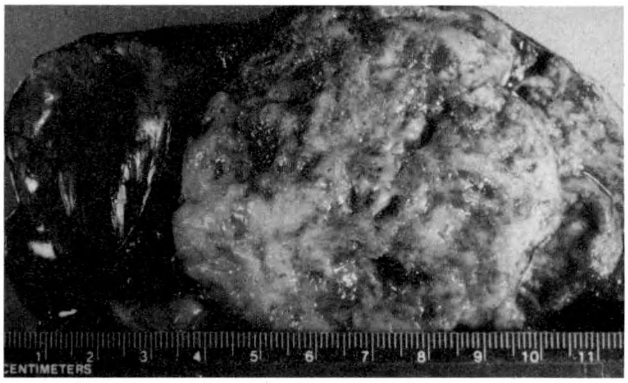

Fig 3. Gross pathological findings of tumor demonstrated in left lower lobe specimen.

Though survival figures vary from reports of limited series of these patients, and certainly long-term survivors are seen, in general, median survival is about 1 year. In 80% of these cases, the tumor is resectable at diagnosis; an operation is the major modality of treatment with radiation reserved as palliation and chemotherapy as adjunct in certain cases. However, distant metastases will eventually occur in more than 40% of patients offered operation [3].

Our report describes a clinical presentation of hypertrophic pulmonary osteoarthropathy as the lead point in diagnosing this patient's carcinosarcoma [7]. The lack of extrapulmonary spread of this tumor and the absence of lymph node involvement may yield a better prognosis for this patient than generally reported as most reports involve tumors of higher stage. At 6-month follow-up, there remains no evidence of metastases or tumor recurrence. The patient's symptoms referrable to hypertrophic pulmonary osteoarthropathy have diminished substantially as has the radiographic severity of this process.

For a tumor to be considered a carcinosarcoma, both malignant epithelial (carcinomatous) and mesenchymal (sarcomatous) elements must be present as documented in this tumor by light microscopy, electron microscopy, and immunohistochemical staining. The histogenesis of carcinosarcoma has been a subject of debate in the pathology literature [1, 8]. Multidirectional differentiation yielding carcinomatous and sarcomatous elements from the same undifferentiated endodermal precursor cell appears to hold more adherents than the rival concept of two separate malignant elements coalescing after independent transformation (collision tumor) [8]. In older literature, light microscopy had been the sole device used to evaluate the mesenchymal portion of these tumors (the spindle cell or sarcomatous portion). In some instances, this technique lacks sufficient specificity in differentiating the sarcomatous stroma of a true carcinosarcoma from the spindle-cell variant of a squamous cell carcinoma [1, 8, 9], which would not accurately reflect survival prognosis for true carcinosarcoma alone. Specifically, immunohistochemical techniques and electron microscopic ultrastructural analysis are required to verify carcinosarcoma. As universal criteria become available to classify these tumors, accurate survival data can be generated.

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Hemolysis Due to Branch Pulmonary Stenosis After the Arterial Switch Procedure

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An infant with d-transposition of the great arteries underwent arterial switch operation using the modified Jatene technique. Severe bilateral branch pulmonary artery stenosis and mechanical hemolysis subsequently developed. The hemolysis resolved after surgical repair of the stenotic arteries. Probable causes are discussed.

(Ann Thorac Surg 1991;51:491–2)

The arterial switch operation of Jatene and colleagues [1] has become the procedure of choice for infants with dextro-transposition of the great arteries at many institutions. In recent years, generally favorable results have been reported [2–5]. Certain well-described complications continue to occur, including supravalvar pulmonary stenosis, left ventricular outflow obstruction, neocoarctation, and kinking of the coronary arteries [2–7]. We describe a unique secondary complication of branch pulmonary artery stenosis after the arterial switch procedure.

A 3.5-kg cyanotic male newborn was diagnosed by echocardiography and cineangiography as having d-transposition of the great arteries. Rashkind balloon atrial septostomy was performed on the second day of life and arterial switch procedure, on the third day, using the Lecompte modification of the Jatene technique [6]. Under deep hypothermia and circulatory arrest, the atrial septal defect was repaired primarily. The aorta and pulmonary artery were transected, and the pulmonary artery was brought anterior to the aorta. The coronary ostia were excised with buttons of aortic wall and were sutured in place on the neoaortic root. The proximal pulmonary artery (neoaorta) was anastomosed to the distal ascending aorta. The proximal aorta (neo–pulmonary artery) was reconstructed with a Gore-Tex patch and attached to the distal main pulmonary artery with an end-to-end anastomosis. The postoperative course was unremarkable, and the child was discharged from the hospital on the seventh postoperative day.

At 11 weeks of age the child was readmitted to the hospital with rhinitis, cough, tactile fever, fussiness, emesis, and jaundice. He had mild hepatomegaly and no splenomegaly. There was a harsh, grade 4/6 systolic ejection murmur. Laboratory data included: hemoglobin, 0.042 g/L; hematocrit, 0.12; white blood cell count, 16.6 × 10^9/L (16,600/μL); and platelet count, 399 × 10^9/L (399,000/μL). Peripheral blood smear showed anisocytosis, poikilocytosis, microspherocytes, schistocytes, polychromasia, and a reticulocyte count of 0.20. Total serum bilirubin level was 51.3 μmol/L (3.0 mg/dL) (normal, 3.4 to 25.7 μmol/L). Aspartate aminotransferase level was 282 U/L (normal, 10 to 40 U/L), and alanine aminotransferase level was 37 U/L (normal, 5 to 25 U/L).

Two-dimensional echocardiography showed a normal pulmonary outflow tract with distal narrowing of the pulmonary artery. Continuous-wave Doppler interrogation showed a flow velocity of 4.5 m/s reflecting approximately an 80-mm Hg pressure gradient.

The child received weekly transfusions of packed red blood cells during the next 4 weeks. During this interval, further hematological evaluation was carried out, including direct Coomb's test, serum viral antibody titers, and urine culture for cytomegalovirus, all of which were negative. Glucose-6-phosphate dehydrogenase assay was normal.

A second cardiac catheterization showed that the main pulmonary artery pressure was suprasystemic at 110/0 mm Hg. The right pulmonary artery pressure was 33/10 mm Hg. Cineangiography showed severe stenosis of both proximal branch pulmonary arteries with the left more severely affected than the right (Fig 1). The pulmonary anastomosis site was not stenotic.

The child underwent surgical repair of the stenotic portion of the pulmonary artery at 15 weeks of age. The pulmonary artery was noted to be constricted by periductal tissue at the bifurcation, distal to the pulmonary anastomosis site. Under cardiopulmonary bypass, a longitudinal pulmonary arteriotomy was performed along the bifurcation and extended to within 5 mm of the first branch bilaterally. The arteriotomy was patched with a 3.0 × 1.0-cm Gore-Tex patch with running suture of 5-0 Gore-Tex.

The child is currently 7 months old and is off all medications. He has grown well and has no evidence of ongoing hemolysis. His hematocrit is 0.34, and he has not required any blood transfusions since the operation. He continues to have Doppler measurements of a mild to moderate degree of pulmonary artery stenosis.

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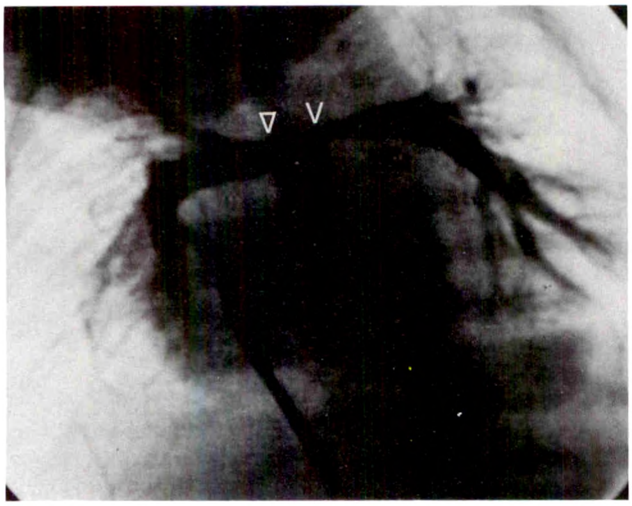

Fig 1. A single frame from a right ventricular cineangiogram (35 mm) demonstrating bilateral pulmonary branch stenosis with the left pulmonary artery (open arrow) *more severely affected than the right pulmonary artery* (closed arrow).

Comment

This case demonstrates several unique features. Supravalvar stenosis, although well described as a postoperative complication of the arterial switch operation for d-transposition of the great arteries, has usually been described as occurring at or proximal to the reanastomosis site [3, 7, 8]. In a large multicenter review of the arterial switch operation, of 12 patients undergoing reoperation for right-sided obstructive lesions, 9 had obstruction in the neo–pulmonary trunk and 3 had valvar stenosis [7]. In another series, 8 of 8 patients who underwent reoperation had stenosis at or proximal to the reanastomosis site [8]. The stenosis in our case occurred at a more distal location; that is, at the bifurcation of the pulmonary artery. The causal mechanism of the stenosis at this location is not known, but we speculate that undue tension on the pulmonary artery owing to the LeCompte maneuver may have played a role. Additionally, there may have been constriction of ductal tissue extending into the pulmonary arteries.

Mechanical hemolysis as a result of cardiac conditions has been well described [9]. Hemolysis has been attributed to a variety of cardiac conditions including prosthetic heart valves, Teflon patches, mechanical pump devices, cardiomyopathy, and endocarditis. Regurgitant valves, primarily aortic or mitral, have also been implicated as causes of hemolysis as has postoperative stenosis of the pulmonary valve. We are unable to find previous reports of mechanical hemolysis due to stenosis of a distal pulmonary artery.

Theoretical considerations put forth by Nevaril and colleagues [10], based on in vitro analysis of shearing forces on red blood cells, indicate that a shearing stress of greater than 3,000 dynes can create hemolysis. They estimate that a 50-mm Hg gradient would be sufficient to generate this amount of shearing force; however, hemolysis is extremely rare despite the relative frequency of pressure gradients greater than 50 mm Hg in our patient population. The unique feature of this case that may have resulted in hemolysis is the presence of a reverse gradient across the stenosis during diastole. This phenomenon could conceivably cause to-and-fro blood flow across an extremely narrow segment, which would predispose to an additional "Waring blender" effect. Surgical intervention, although not completely relieving the stenosis, has decreased its severity and resulted in resolution of the hemolysis. The child does not have any other evidence of a hematological abnormality that would lead to increased fragility of the red blood cells.

Further refinement of surgical techniques for the arterial switch procedure should lead to continued improvement of both short- and long-term outcome in children with d-transposition of the great arteries. Avoidance of undue tension on the pulmonary arteries by liberal mobilization of the distal segment of the transected pulmonary artery is a desirable aspect of the LeCompte maneuver. Awareness of the potential complications, careful postoperative evaluation, and timely intervention to relieve major obstructions are necessary.

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Surgical Management of Carcinoid Heart Disease

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Metastatic carcinoid tumor is often seen with flushing, diarrhea, and cardiac symptoms—the carcinoid syndrome. Cardiac failure is often associated with major morbidity and mortality in carcinoid disease. In this report, a case of successful cardiac valvar surgical intervention has resulted in prolonged alleviation of cardiac symptoms and survival.

(Ann Thorac Surg 1991;51:493–4)

Valvar heart disease and cardiac failure are frequent findings and major causes of morbidity and mortality in patients with carcinoid syndrome. The tricuspid and pulmonary valves are the most common sites of involvement. We report a case of valvar heart disease secondary to the carcinoid syndrome that underwent successful valve operation resulting in alleviation of cardiac symptoms and prolonged survival.

A 36-year-old woman was seen with intractable cardiac failure. Thirty months before this, she was seen with a 12-month history of lethargy, dyspnea, palpitations, wheezing, hot flushes, and diarrhea. Investigations at that time showed marked hepatomegaly and elevated levels of serum 5-hydroxytryptophan and urinary 5-hydroxy indoleacetic acid excretion. A liver biopsy confirmed metastatic carcinoid tumor, the primary site not being identified. She was treated with cryptoheptadine, ketanserin, and tamoxifen with resulting alleviation of her symptoms. However, on this occasion, increasing symptoms of disabling cardiac failure unresponsive to medical therapy resulted in further investigation.

On examination, she was plethoric and centrally cyanosed. Her blood pressure was 97/70 mm Hg and she was in sinus rhythm. The jugular venous pressure was elevated at 8 cm H_2O, with prominent tricuspid regurgitant waves. Marked peripheral edema was extending up to the lower abdomen. A systolic ejection bruit (3/6) was audible at the pulmonary valve. Her lung fields were clear. Fourteen centimeters of irregular, pulsatile hepatomegaly was palpable, and ascites was present.

Echocardiography showed a thickened tricuspid valve and a moderate right atrial and right ventricular hypertrophy with dilatation. Left ventricular function was normal. An injection of a contrast medium showed a right to left shunt at atrial level. The pulmonary valve was not visualized.

Cardiac catheterization demonstrated a dilated right ventricle with gross tricuspid incompetence (V wave, 34 mm Hg) and thickened tricuspid valves. A right atrial to right ventricular gradient of 8 mm Hg was present. Pulmonary valve stenosis with a peak systolic gradient from right ventricle to pulmonary artery of 28 mm Hg was present. Pulmonary valve stenosis with a peak systolic gradient from right ventricle to pulmonary artery of 28 mm Hg was present. Evidence of a right to left shunt was not obtained. Cardiac surgical intervention was decided on.

Operative Findings and Procedure

At operation, the right atrium was tense and dilated, with thickened wall. On opening the right atrium and main pulmonary artery, the tricuspid valve was grossly thickened and the anterior leaflet was contracted with chordal shortening. The pulmonary valve was grossly thickened, and the orifice measured 3 mm in diameter. There was no macroscopic evidence of subendocardial thickening of the right ventricle.

The tricuspid valve was excised and replaced with a size 27 St. Jude prosthesis. The pulmonary leaflets were excised back to the annulus. Prosthetic valve implantation in the pulmonary annulus was not performed, and the annulus, measuring 20 mm in external diameter, was not enlarged. Cardiopulmonary bypass was withdrawn without difficulty. A residual right ventricular–pulmonary artery gradient of 20 mm Hg was present with satisfactory hemodynamic performance. Transient heart block, which required temporary ventricular pacing before returning to sinus rhythm, and mild renal impairment, which responded to diuretic and fluid therapy, occurred in the postoperative period.

Pathology

The endocardial surface of the heart was covered in plaques consisting of fibrous tissue free of elastic fibers, which were sharply demarcated from otherwise normal underlying endocardium by the elastic lumina. Similar plaques were also found on the valves (Fig 1). Cellular infiltration of the fibrous tissue was not marked.

The pathological changes tended to occur on the arterial (distal) side of the pulmonary cusps. The tricuspid valve was affected on both sides with involvement of the chordae tendinae, which were shortened and thickened.

Progress

At the last follow-up visit 70 months after operation, the patient was in sinus rhythm and was free of cardiac and carcinoid symptoms. Her medications at this time included 0.25 mg of digoxin to be taken in the morning, 40

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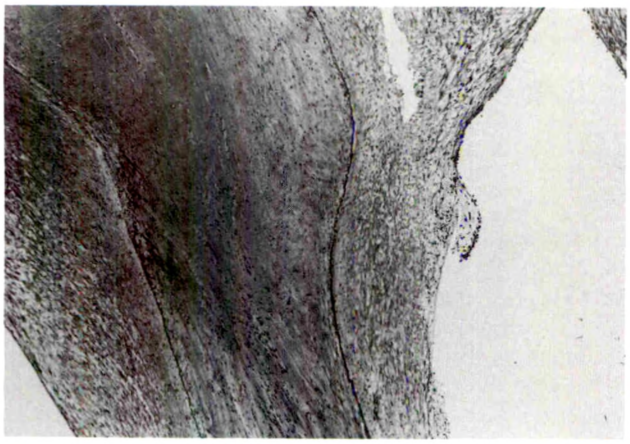

Fig 1. Section of tricuspid valve showing fibrous plaque on both surfaces. (Hematoxylin and eosin, ×60 before 50% reduction.)

mg of Lasix (furosemide) to be taken in the morning, 100 mg of Aldactone (spironolactone) to be taken in the morning, 3 mg of warfarin to be taken in the evening, 4 mg of cryptaheptadine hydrochloride four times a day, 10 mg of ketanserin three times a day and 20 mg of tamoxifen twice a day.

A chest roentgenogram showed normal heart size and pulmonary vasculature. A liver scan showed the appearance of a new nodule in the right lobe.

Comment

Long-term survival with metastatic carcinoid disease occurs, although 50% of patients have cardiac failure, causing death in 30% of these patients [1].

After the original failed attempt at surgical correction of the carcinoid heart by Wright and Mulder in 1963 [2], Aroesty and colleagues [3] reported successful tricuspid valve replacement in a patient with carcinoid heart disease. The patient lived 6 years and died of hepatic metastasis. In 1971, Garcia and co-workers [4] excised only the pulmonary valve (the tricuspid incompetence thought to be secondary to right ventricular dilatation) with a fatal outcome. Others have reported long-term survival after tricuspid valve replacement and pulmonary valvotomy [5]. Okada and associates [6] reported a successful outcome after porcine heterograft replacement of tricuspid valve and pulmonary valvectomy were performed, and the patient was alive 4 months after operation. Our patient has a 70-month symptom-free survival with essentially normal lifestyle.

Although cardiac surgeons favor replacement of the tricuspid valve with a bioprosthesis, we used a mechanical prosthesis because of the theoretic potential for carcinoid disease to affect the bioprosthetic valve leaflets in a similar fashion to the native valve. Miller and colleagues [7] have referred to this possibility but as yet it has not been reported.

Pulmonary valve replacement is less than satisfactory and a plastic-type procedure such as valvotomy, excision of a cusp or a whole valve, or widening of the outflow tract with a patch is preferred. Most of these procedures leave residual pulmonary insufficiency, which is usually well tolerated if severe right ventricular failure has not occurred. Even with moderate right ventricular failure, the degree of pulmonary insufficiency and residual pulmonary outflow gradient in our patient is well tolerated. Surgical correction of the valvar lesions has resulted in a much improved lifestyle, with a long period of survival. Hence, an operation should not be withheld from these patients purely on the grounds of incurable metastatic disease.

Addendum

The patient remains well, 85 months after operation.

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False Aneurysm Formation of the Great Arteries After Arterial Switch Operation

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An infant with simple transposition of the great arteries underwent a two-staged arterial switch operation, after which mediastinal infection occurred. Continuous irrigation with povidone-iodine solution was performed for 10 days. After that, the patient experienced life-threatening hemorrhage three times. At the time of the second hemorrhage, greater omental transfer was performed. On postoperative day 109, false aneurysm was recognized, having developed from both great arteries. Successful repair was performed on postoperative day 110.

(Ann Thorac Surg 1991;51:495–6)

Purulent mediastinitis is a devastating complication after median sternotomy. We had 1 case with formation of a false aneurysm of the great arteries after control of mediastinal infection following the arterial switch operation.

An 11-month-old, 7.1-kg infant with simple transposition of the great arteries, who had previously undergone pulmonary artery banding and modified Blalock-Taussig shunt at the age of 7 months, underwent the arterial switch operation under profound hypothermia and low-flow perfusion. A neoaorta was reconstructed by the Lecompte maneuver [1] using a continuous running suture of 5-0 Prolene (Ethicon, Somerville, NJ). A neopulmonary arterial trunk was then reconstructed with 6-0 Prolene suture. The aortic cross-clamp time was 137 minutes. The cardiopulmonary bypass time was 453 minutes. The sternum was left open owing to ventricular swelling. The wound was closed with a polytetrafluoroethylene soft tissue patch. Peritoneal dialysis for subsequent renal failure and administration of an arterial vasodilator and moderate doses of inotropic support were necessitated.

On postoperative day (POD) 5, the sternum was closed. However, on POD 7, white blood cell count and C-reactive protein level were increased to 17.8 × 10^9/L (17,800/μL) and 12.7 mg/dL, respectively, with purulent discharge in the drainage tube. The patient was taken to the operating room for mediastinal reexploration, debridement of all necrotic and grossly infected tissue, irrigation, and placement of two mediastinal tubes for irrigation. The sternum was closed with stainless steel wires. *Staphylococcus aureus* was cultured from arterial blood and from purulence in the mediastinum. Continuous mediastinal irrigation at the rate of 20 mL/h with 0.5% povidone-iodine solution diluted in normal saline solution was begun. Antibiotics to which the organism was susceptible were administered intravenously. Ten days after the irrigation, because the cultures showed no growth from the mediastinal fluid and arterial blood, the irrigation was discontinued.

On POD 22, the patient had a sudden gush of blood from the drainage tube and was taken to the operating room promptly. The perforation was located at the right main pulmonary artery near the bifurcation, which was considered to be eroded by the irrigation tube. The ruptured site was repaired using a porcine pericardial patch under mild hypothermic cardiopulmonary bypass. On POD 33, the infant suddenly hemorrhaged from the wound again. The ruptured site was on the anterior wall of the neoaorta just below the anastomosis line, between two implanted coronary buttons. Under profound hypothermic cardiopulmonary bypass, the hole was closed with two mattress sutures using 4-0 Prolene with a small pledget. Transfer of the greater omentum was performed. On POD 35, the patient had repeated massive hemorrhage. There was a ruptured site between the previously repaired site and the left coronary button in the anterior wall of the neoaorta. The ruptured site was repaired with small felt strips and two interrupted mattress sutures under profound hypothermic cardiopulmonary bypass. The greater omentum was replaced on exposed vessels and the heart.

On POD 90, roentgenograms of the chest began to show a growing mass that occupied the mediastinum. The right heart failure progressed with enlargement of the mass. On POD 109, angiography and color-mapping Doppler echocardiography documented that the mass was a false aneurysm formed from not only the neopulmonary arterial trunk but also the neoaorta. On POD 110, after an arterial cannula was inserted through the femoral artery and venous cannulas through the internal jugular vein and the femoral vein, core cooling was started. When

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the rectal temperature was lowered to 22°C, median sternotomy was done. The anterior wall of the false aneurysm consisted of the transferred greater omentum. The right atrium was compressed posteriorly and caudally. There were two ruptured sites in the kissing position, which were located between sites of previous repairs in the neoaorta and in the posterior wall of neopulmonary arterial trunk, respectively. After transection of the neopulmonary arterial trunk, the former hole was repaired using equine pericardium reinforced with a Dacron fabric patch. The pulmonary arterial trunk was reconstructed with equine pericardial roll. The postoperative course was uneventful except for left phrenic nerve palsy, requiring plication of the left diaphragm. The patient was extubated on POD 172 and was discharged on POD 291 with mild brain damage.

Comment

False aneurysm after pediatric cardiac operations has been reported in several articles [2–4]. Arterial switch operation requires many suture lines. Therefore, mediastinitis might cause life-threatening hemorrhage from exposed mediastinal vessels. In our patient, the first hemorrhage was caused by perforation of the right pulmonary artery, which was mainly considered to be eroded by the tip of the irrigation tube. The other ruptured sites were not at the suture lines, but near those suture lines using nonabsorbable suture material. These sites were located in the proximal neoaorta, which had been the proximal pulmonary arterial trunk before arterial switching. Sievers and associates [5] reported that the wall of the anatomical pulmonary artery proximal to the pulmonary artery banding showed the aortic configuration of medial elastic fibers. Therefore, the perforations of the proximal neoaorta might have been caused by infection or mechanical stress, not by weakness of this wall structure.

For management of mediastinitis, some reports [6, 7] have recommended debridement and pectoral muscle flap or greater omentum closure in one stage without continuous irrigation with povidone-iodine or antibiotics. In our case, it is not known whether the initial treatment of purulent mediastinitis using omental transfer might have prevented repeated hemorrhage or formation of false aneurysm postoperatively.

Addendum

In this patient, the fungal masses of the pulmonary artery were removed with the aid of cardiopulmonary bypass on June 7, 1990 (9 months after discharge). He tolerated the operation well. However, the antifungal treatment continues to be performed.

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Adenocarcinoma Arising in a Foregut Cyst of the Mediastinum

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A case of malignant transformation in a mediastinal cyst of the esophageal reduplication type is presented. The cyst had been recognized 39 years previously, but remained asymptomatic until sudden growth occurred. It was resected totally from the esophagus and the patient recovered well. A review of the literature showed that malignancy in mediastinal foregut cysts is extremely rare.

(Ann Thorac Surg 1991;51:497–9)

Primary mediastinal tumors comprise a broad spectrum of lesions. Among the mediastinal cystic lesions, a small group of primitive foregut derivatives are found. In this paper, a case of adenocarcinoma arising in an intraesophageal duplication cyst is presented. The literature concerning nondiverticular but true cystic mediastinal tumors has been reviewed, and the strategy to manage these lesions is discussed.

A 61-year-old man was admitted for surgical removal of a mediastinal tumor. Forty years previously, the lesion had been recognized as a cyst. It had been asymptomatic and appeared unchanged on control roentgenograms for many years. Due to sudden growth and pain, the patient was referred to us (Fig 1). Through a right thoracotomy, a cyst of approximately 1,500 mL was totally excised. The cyst was in contiguity with the esophageal wall, from which it had to be divided by sharp dissection, but there was no attachment to other structures.

Gross appearance of the specimen was that of a well-circumscribed cyst measuring 5 × 8 × 14 cm with a smooth outer surface and a frayed, necrotic inner lining. It contained a brownish, cloudy, serous liquid. Its wall was solid with a thickness of 1 to 2 cm. Microscopic examination showed a varying luminal epithelial lining—simple cuboidal to a well-differentiated ciliated respiratory type of epithelium (Fig 2A). Focally, the epithelium was of immature intestinal type—cylindrical, nonciliated with a few goblet cells. In other areas, the epithelium appeared dysplastic, and there was focal ulceration. In the surrounding wall, foci of well-differentiated adenocarcinoma were found (Fig 2B). The wall had an intestine-like structure with a submucosal layer and a peripheral double layered muscular coat. There were distinct ganglionic plexuses. The carcinoma invaded the outer muscular layer, but was not observed beyond it. No cartilage or bronchial glands were found. The cyst was classified as an esophageal reduplication cyst according to accepted criteria, *vide infra*, with a well-differentiated adenocarcinoma. The resected lymph nodes were without metastases.

The postoperative course was uneventful, and the patient was in good condition at follow-up 2 months later.

Comment

Thoracic cysts derived from the primitive gut are categorized as gastroenteric, bronchogenic, and esophageal reduplication cysts. The gastroenteric type is thought to arise in embryonic life from adherence of the endodermal tube to the notochord, and during growth, a traction diverticulum is formed, which later develops into a gastroenteric cyst [1–3]. These cysts are often attached to the spine, and a great proportion is associated with vertebral malformations [3]. They are practically never in contiguity with the esophagus [1].

The respiratory system arises in the early embryonic life from a ventral outgrowth of the primitive foregut. Bronchogenic cysts are considered to be supernumerary lung buds [2], and they are often lined with ciliated columnar epithelium and have cartilage in the wall [1].

The esophageal reduplication cysts, too, arise from the primitive foregut, which in the early embryonic life is a solid tube. Later, vacuoles arise and fuse to form the lumen. Esophageal duplication cysts are thought to evolve from isolated vacuoles that fail to fuse with the lumen [1, 2]. Distinction between bronchogenic and esophageal duplication cysts may be difficult, and esophageal reduplication cysts often are lined with respiratory as well as esophageal epithelium as in the present case. The presence of a double layer of smooth muscle in the cyst wall without any cartilage classifies the cyst as esophageal [2]. Our case satisfies these criteria.

We have found few reports of malignancy in thoracic cysts unequivocally derived from the foregut [4, 5]. One was an adenocarcinoma in a pedunculated cyst from a 41-year-old man. The pedicle was attached to the fourth costovertebral angle, and consequently, it was classified as a gastroenteric cyst [4]. Another report is of a squamous cell carcinoma in an esophageal sac-like structure in a 63-year-old man. In spite of communication to the esophageal lumen, a double layer of smooth muscle in

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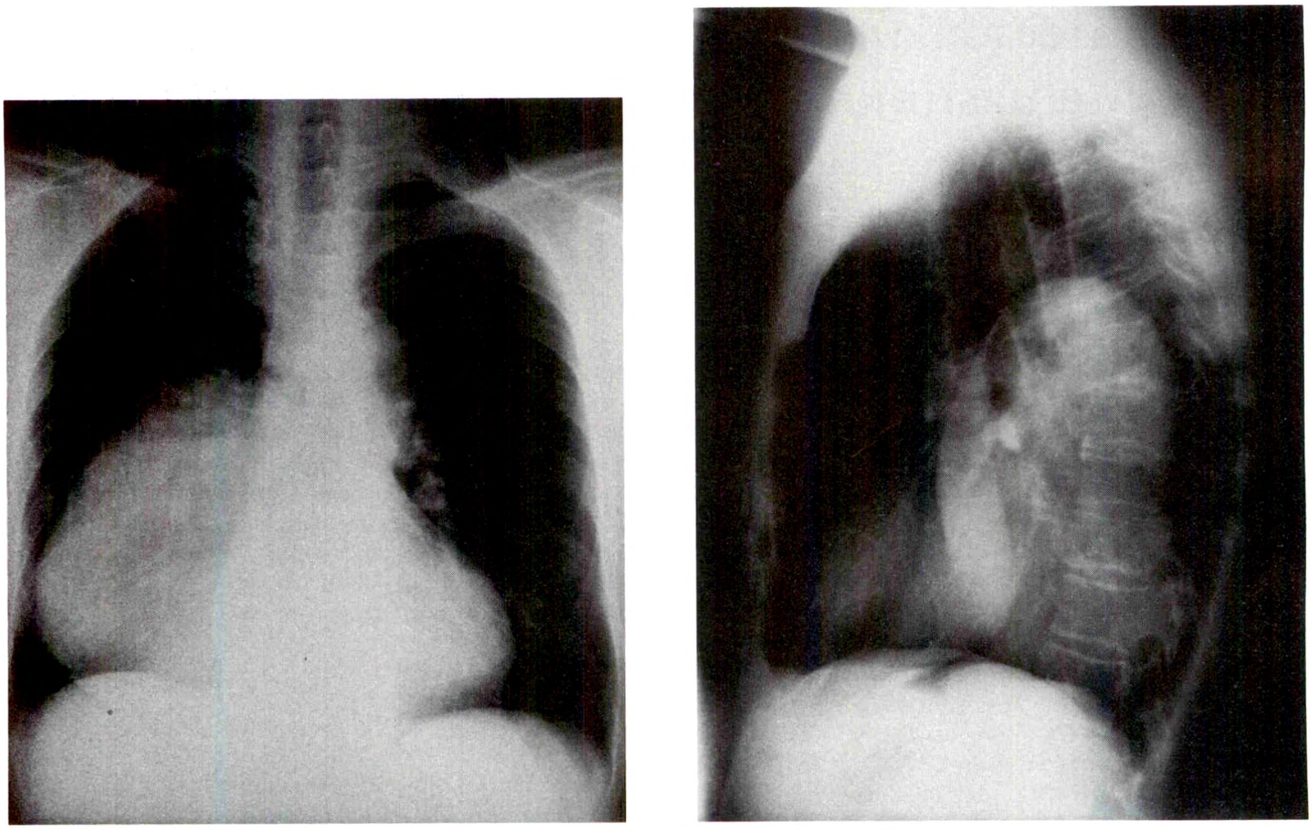

A B

Fig 1. Preoperative chest roentgenogram in anterior (A) and lateral (B) views shows the rounded mass protruding into the right hemithorax.

the wall was suggestive of a duplication cyst rather than a diverticulum [5].

Additional cases of malignancy in intrathoracic cysts have been reported, but exact classification of the cysts is unsettled: At autopsy of a 65-year-old man, an intramural cystic tumor was found in the deep submucosa and muscularis propria of the esophagus [6]. It was lined by squamous epithelium of esophageal type focally in continuity with an invasive squamous cell carcinoma. Between the cyst and the luminal normal esophageal squamous epithelium, there were nests of normal squamous and transitional epithelium, indicating an inclusion cyst origin of the process, rather than a developmental cyst. Another case [7] was an adenocarcinoma in a small polyp, protruding from the luminal surface of a cyst in the anterior mediastinum of a 48-year-old woman. The cyst was lined with "enteric epithelium," but its relation to the esophagus was not described, and the cyst cannot be classified with certainty.

In contrast to the rarity of malignancy in these primitive foregut cysts, 42% of all mediastinal tumors are malignant [8]. In addition, the close relation to vital mediastinal structures leaves these cysts potentially dangerous. Operation therefore has been strongly recommended in mediastinal tumors [1].

Despite the extreme rarity of malignancy in mediastinal cysts, the only definite diagnosis is obtained by thoracotomy, and resection of mediastinal cysts should always be considered when diagnosed.

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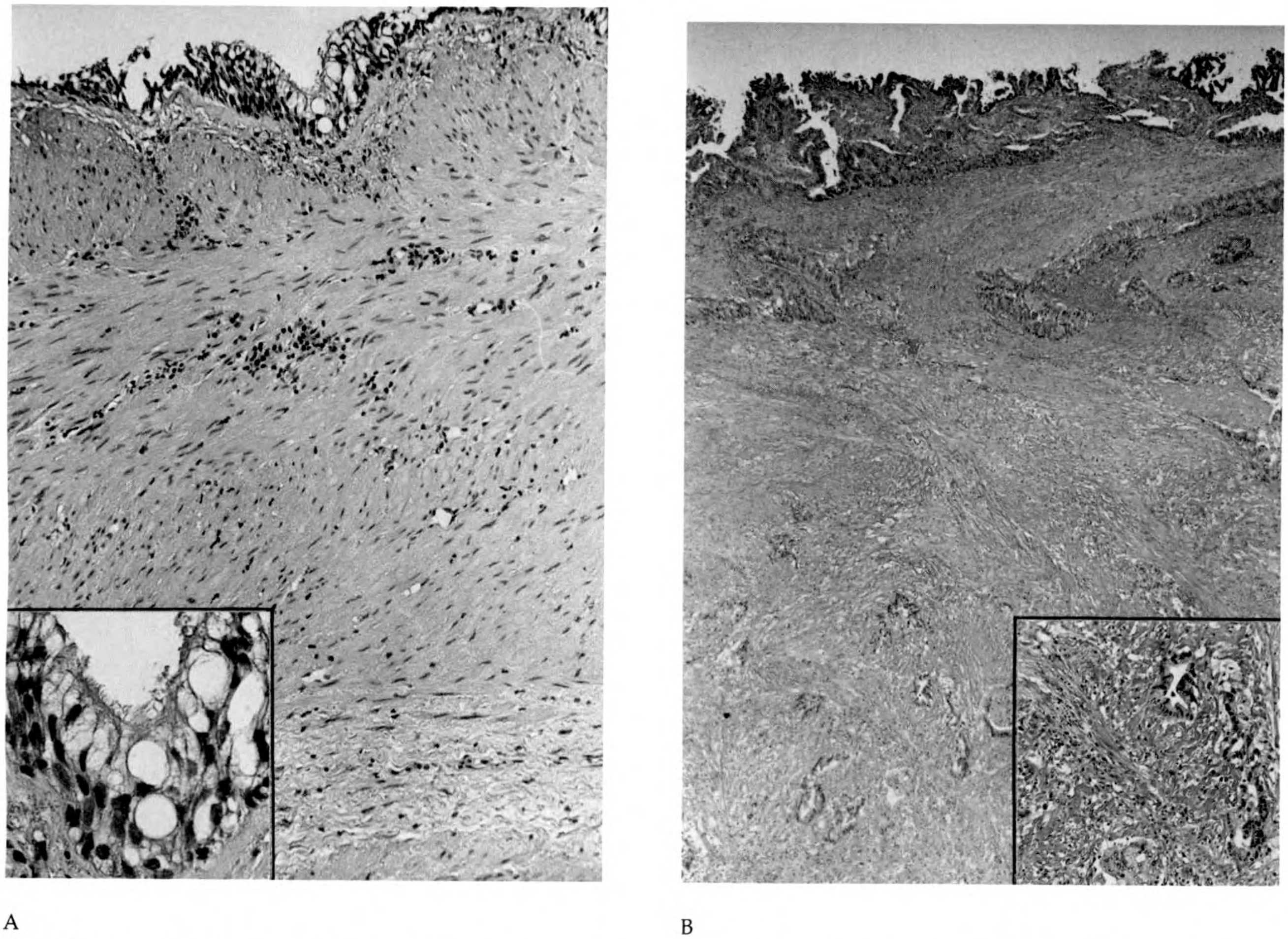

Fig 2. The cyst wall has an intestine-like structure and is composed of smooth muscle fibers in perpendicularly oriented layers (A). The luminal surface is lined by respiratory-like epithelium (inset). In other foci the wall is infiltrated by an adenocarcinoma (B). (Hematoxylin and eosin, A, ×100 (×250, inset) before 8% reduction; B, ×100 (×25, inset) before 8% reduction.)

Mammary Artery Grafts: A New No-Touch Technique for Anastomosis

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Reported techniques for mammary artery–coronary artery anastomosis involve instrumental damage to one or all three layers of the mammary artery during surgical connection. Described herein is an atraumatic method of suturing that achieves a precise and highly accurate anastomosis.

(Ann Thorac Surg 1991;51:500–3)

Despite widespread acclaim and the emerging evidence regarding the superiority [1–3] of the mammary artery as a conduit for coronary revascularization, universal acceptance by surgeons has not occurred. It is an interesting and curious fact that despite all that has been written about mammary artery grafts over the past 20 years, in only 36.9% of coronary operations in the US are mammary arteries routinely employed [4]. Of the 243,000 coronary operations performed in the US in 1987, the proportion involving single internal mammary–coronary artery bypass grafts was 31.6% and double internal mammary–coronary artery bypass grafts, 5.3%. This confusing contradiction between surgical practice and the accepted virtues of the mammary artery graft confirms the obvious: factors other than the mammary artery, the so-called lasting conduit [1], influence the surgeon. Although some have brought mammary artery grafting to state-of-the-art perfection [1, 5], others find graft harvest laborious and time consuming and the anastomosis of this vasoactive artery either unsatisfactory or technically difficult.

Mammary arteries, being friable conduits, poorly tolerate instrumental handling. Mammary artery–coronary artery anastomosis as commonly performed necessarily involves holding either the adventitia or the full thickness of the mammary artery with a forceps at its cut end to stabilize the tissue for suturing. The artery is often held circumferentially in different places by the surgeon or the assistant while the anastomosis is performed. The common practice of excluding the traumatized areas from the anastomosis by stitching them out makes for a smaller than desirable anastomosis and may lead to late anastomotic stricture. Apart from trauma there is a need for a good method to stabilize and expose the vessel for expeditious and accurate suturing. The approach presented here, including a novel atraumatic technique at the anastomosis, overcomes these problems.

Material and Methods

Technique of Harvest and Preparation

The internal mammary artery is harvested on a pedicle after two parallel diathermy tracks are made along the inner chest wall 1.0 cm on either side of the artery along its entire length. Using low-intensity electrocautery, a dissecting diathermy spatula is then used to separate the mammary pedicle from the chest wall in a medial to lateral direction. When the pedicle hangs loose but is still attached at both ends, careful inspection of its upper aspect is made and the intercostal vessels are identified and clipped with a titanium clip applicator. The vessel is then lavaged with papaverine and wrapped in a soaked gauze pad while cannulation takes place.

Before the commencement of bypass, the distal aspect of the mammary artery is divided and the pedicled vessel is laid longitudinally on a large gauze pad on top of the heart. A small Dietrich clip is applied transversely at the level of the mid portion of the pedicle (Fig 1A). The distal pedicle and clip are now rotated 180 degrees clockwise (Fig 1B). The distal aspect of the pedicle now has its muscular surface uppermost. The assistant now holds the end of the mammary artery in a downward manner with a fine forceps in the left hand while holding the muscular aspect of his or her side of the pedicle with a forceps in the right hand (Fig 1C). The surgeon holds the other side of the muscular pedicle and with sharp scissors cuts longitudinally for 3.0 cm, bifurcating the muscle and exposing clearly the vessel itself (Fig 1D). The muscle on both sides is now trimmed from the vessel. A coronary scissors is now introduced into the lumen of the vessel and a 2.0-cm proximal arteriotomy is made. The vessel is now ready for coronary anastomosis. At this point a dilute papaverine [6] and blood solution is injected up the mammary lumen while the artery clip is repositioned to the distal aspect of the muscular pedicle to allow the vessel to vasodilate before anastomosis.

No-Touch Technique of Anastomosis

The distal mammary artery now projecting from the muscular pedicle is denuded, longitudinally arteriotomized on its muscular side, and redundant. This redundant portion of the vessel is for handling and is removed

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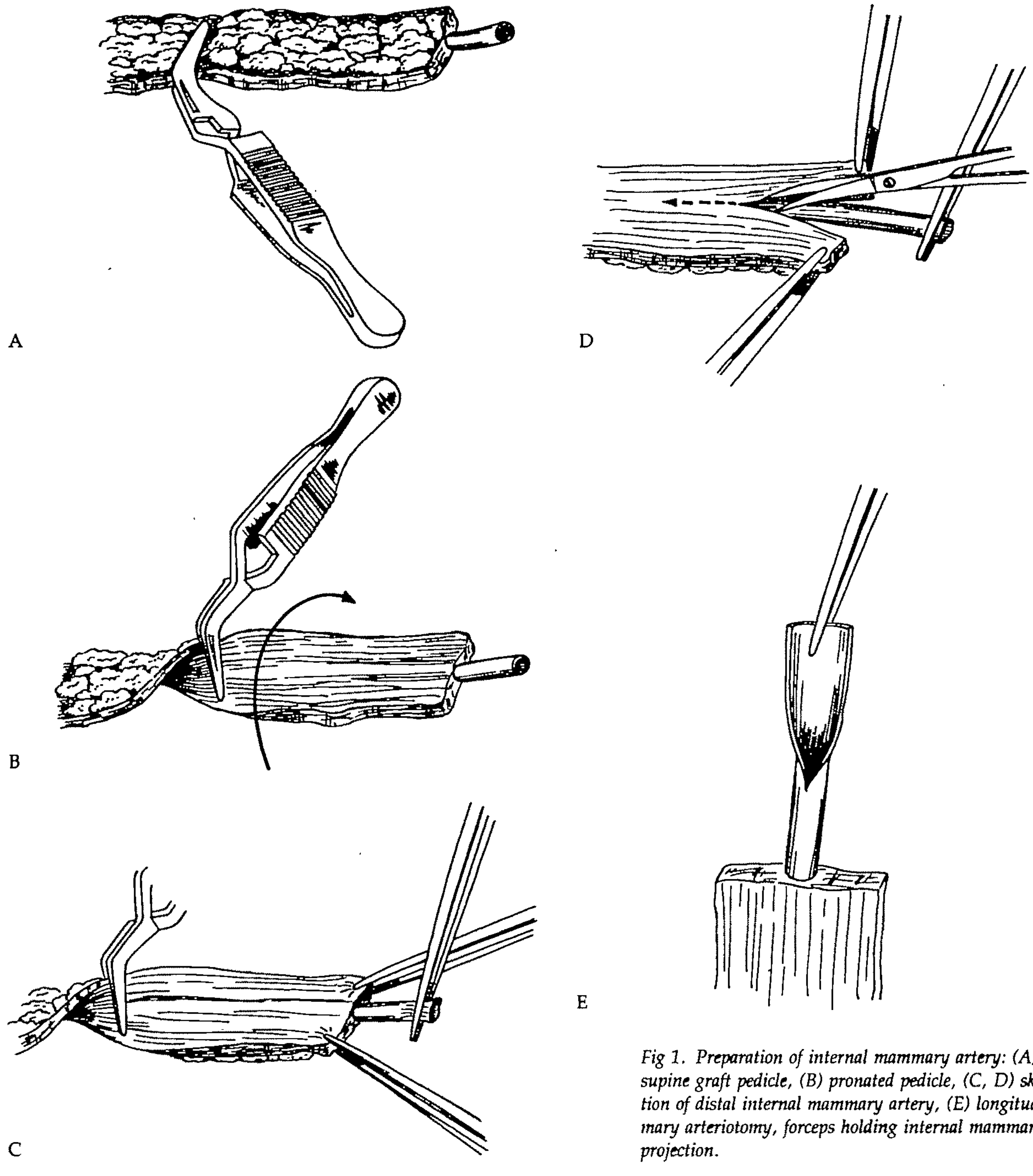

Fig 1. Preparation of internal mammary artery: (A) harvested supine graft pedicle, (B) pronated pedicle, (C, D) skeletonization of distal internal mammary artery, (E) longitudinal mammary arteriotomy, forceps holding internal mammary artery projection.

during the anastomosis. The assistant first holds the vessel with the forceps so it hangs from the left-sided chest drapes by its pedicle into the pericardial cavity (Fig 1E). The weight of the pedicle and the assistant's hold on the artery stabilize the vessel in a very satisfactory fashion for the surgeon, who now places the first suture one stitch distance from the heel of the mammary arteriotomy (Fig 2A). A running mammary artery–coronary artery suture is done with the mammary artery in the held-up position and goes from outside the mammary artery in, in a counterclockwise fashion to one stitch distance on the other side of the heel.

The vessel is now lowered into position as both ends of the 8-0 Prolene suture are pulled taut (Fig 2B). This completes the heel of the anastomosis without surgeon or assistant ever catching the cut aspect of the sutured vessel that is connected to the coronary artery. The surgeon now holds the distal aspect of the redundant mammary artery with forceps in the left hand and quickly does a running suture down the right aspect of the anastomosis. When he or she is two stitches from the toe of the anastomosis, he or she diagonally cuts *ab*, the redundant remaining mammary artery, in a 45-degree fashion (Fig 2C). The surgeon completes the anastomosis as far as the toe *b* by catching the projecting redundant mammary angle *c* (Fig 2D). When the toe stitch is inserted a second oblique mammary

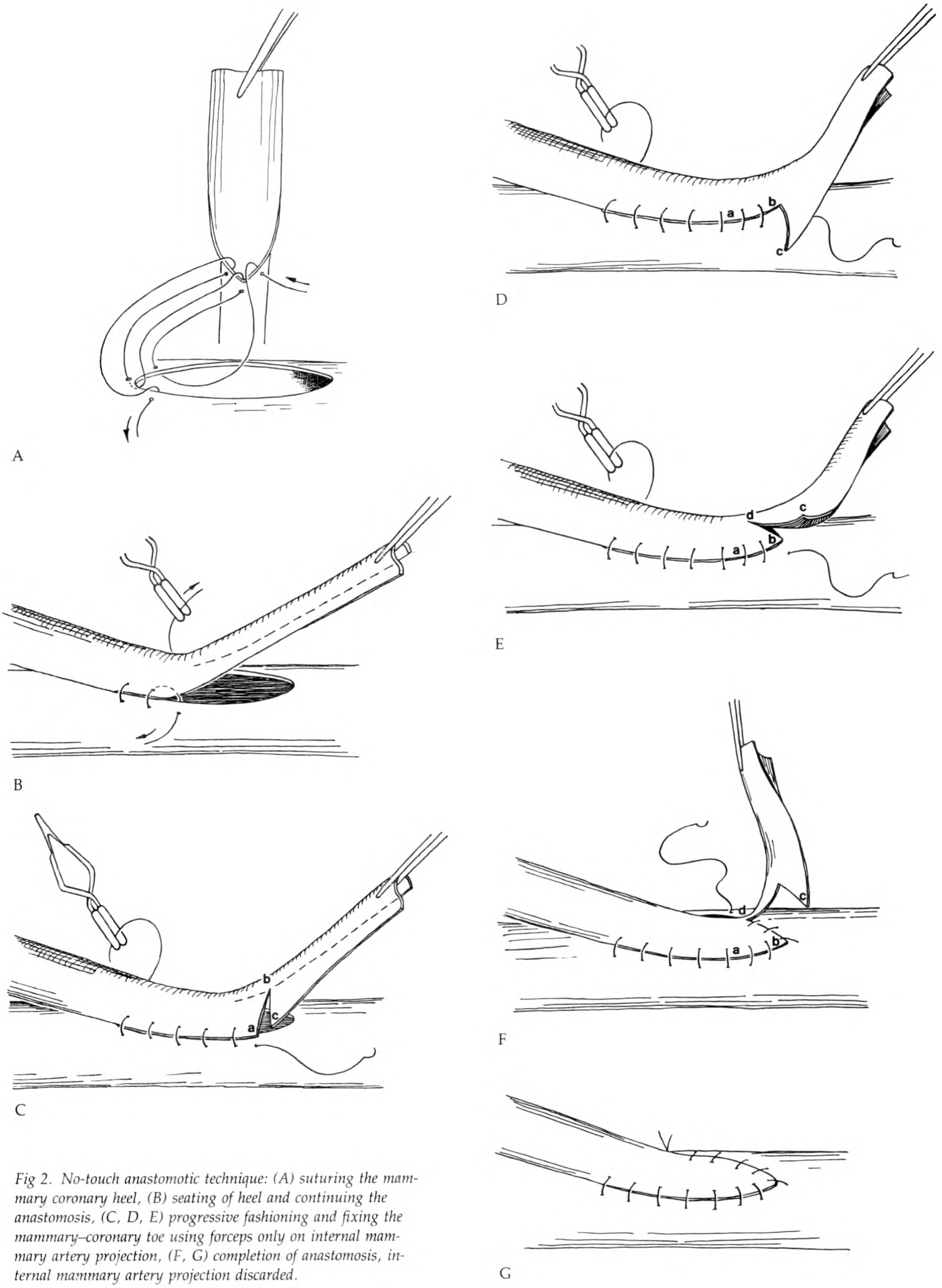

Fig 2. No-touch anastomotic technique: (A) suturing the mammary coronary heel, (B) seating of heel and continuing the anastomosis, (C, D, E) progressive fashioning and fixing the mammary–coronary toe using forceps only on internal mammary artery projection, (F, G) completion of anastomosis, internal mammary artery projection discarded.

arteriotomy (*bd*) is made (Fig 2E), and the redundant portion of the artery is progressively removed while a continual running suture easily completes the anastomosis (Fig 2F) without any instrumental damage to the implanted mammary artery. The mammary clip is momentarily released to allow coronary filling and anastomotic expansion as the knot is tied (Fig 2G).

Comment

Some surgeons are reluctant to employ mammary artery grafts because of past experiences with vasospasm or because they find them technically demanding [2]. Reported results [1, 5, 7–9] and patency rates for mammary artery grafts widely vary. Poor results may be due to inappropriate selection [5, 7, 9] of patients for mammary grafting, damage to the pedicle during harvest [3], external compression due to over-zealous attempts at pericardial closure, and trauma and technical faults at the anastomosis [3]. This atraumatic method of mammary artery handling, the forceps-less approach to the cut aspect of the mammary artery, eliminates damage to the mammary artery at the anastomosis and satisfactorily stabilizes the vessel for suturing.

It is hoped that this paper will encourage those who still have doubts about the mammary artery graft and who would like a method that is quick and easy to perform, is atraumatic, and gives high-quality exposure and reproducible results.

Appreciation and thanks are expressed to Marcus Cremonese (Department of Medical Illustration, Prince of Wales Hospital, Sydney) for artwork.

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Silicone Pouch for Protection of Automatic Implantable Cardioverter-Defibrillator Leads

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Automatic implantable cardioverter-defibrillator has become routine treatment for recurrent, drug-resistant ventricular tachycardia. Although there is documentation regarding clinical experience and device performance, there is little information on how to avoid complications related to the retrieval of sensing and defibrillation leads from the subcutaneous space. We are reporting our experience with a silicone pouch for protection of automatic implantable cardioverter-defibrillator leads that allows immediate and simple retrieval of the leads in case an automatic implantable cardioverter-defibrillator generator is needed.

(Ann Thorac Surg 1991;51:504–5)

The value of the automatic implantable cardioverter-defibrillator (AICD) for treatment of recurrent, refractory ventricular tachycardia has been demonstrated [1–6]. Unfortunately it remains difficult to determine which patients are still at high risk for recurrence of malignant ventricular arrhythmia postoperatively. Because of the high cost of the pulse generator and the possibility that the device will be unnecessary postoperatively, some investigators now implant only the patch lead system at the initial operation, followed by postoperative electrophysiological evaluation to determine which patients still require the device. Those patients who do not require it are spared the expense, burden, and potential complications of the device [5, 7–9]. For those patients who require an AICD generator at a later date, its implantation is simplified as the chest does not need to be reentered.

Complications referable to retrieval of wires from the subcutaneous pocket are not mentioned in the medical literature. Chronic implantation of AICD leads is generally accompanied by the development of an excessive amount of fibrotic tissue; the migration of lead wires has been also reported [10]. For those patients who later require implantation of the pulse generator, retrieval of the lead wires is often hindered, necessitating extensive subcutaneous dissection with possibility for accumulation of seromatous fluid. In these circumstances, extensive dissection increases the risk of damage to the wires and makes an otherwise simple operation an exercise in tedium. Thus, we devised a silicone pouch in which to store the wires within the subcutaneous pocket. This report describes our experience with patients undergoing late implantation of AICD in whom a silicone pouch for protection of patch lead wires was used.

Material and Methods

From 1987 to 1990, 16 patients (12 men and 4 women) underwent implantation of epicardial patch leads for an AICD at Cooper Hospital/University Medical Center, Camden, NJ, without generator implantation at their initial operation (Table 1). Age at implantation ranged from 40 to 75 years (mean, 63.9 ± 7.8 years). At the initial operation, 10 patients underwent concomitant coronary artery bypass grafting, 1 had coronary artery bypass grafting and aneurysmectomy, 3 had aneurysmectomy alone, 1 had coronary artery bypass grafting and repair of a ventricular septal defect, and 1 had aortic and mitral valve replacement. All patients had the lead wires inserted in a standard manner as previously described [11] and positioned through a tunnel in the left upper abdominal quadrant, beneath the costal arch margin into the subcutaneous space. Seven patients had patch lead wires coiled up in a 6 × 6-cm silicone pouch and inserted into a left upper abdominal quadrant subcutaneous pocket. To construct the pouch, an approximately 12 × 6-cm piece of silicone sheeting was plicated in half. The lateral sides of the pouch were sewn with 3-0 locking Prolene (Ethicon, Somerville, NJ) sutures. After the introduction of the wires into the pouch, the fourth side of the quadrant was closed with interrupted 3-0 Prolene suture. Skin was closed in an anatomical fashion.

All 16 patients underwent postoperative electrophysiological evaluation to determine the subsequent need for generator implantation. Ten patients received the AICD pulse generator (Cardiac Pacemaker, Inc, St. Paul, MN) at a later date. This modality was chosen for 8 patients with drug-refractory ventricular tachycardia and 2 patients with sudden death syndrome. At the time of implantation of the AICD generator, the silicone pouch was entirely removed with no difficulties. There was no additional time necessary for dissection and removal of the pouch. The time interval between the initial operation and the

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Table 1. Operative Data

Concomitant Procedure	No Silicone Pouch	Silicone Pouch
CABG	5 (4)[a]	5 (4)
CABG + aneurysmectomy	1	0
Aneurysmectomy	2	0
CABG + VSD	1	1 (1)
AVR + MVR	0	1 (1)
Total	9 (4)	7 (6)

[a] Parentheses show the number of patients receiving the AICD generator at a later date.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; VSD = ventricular septal defect.

implantation of the AICD generator was 65.5 ± 71.4 days for patients without a silicone pouch versus 97.5 ± 89.4 days for those with a silicone pouch ($p = 0.572$). SPSS Plus (version 3.0) was used for statistical analysis. Independent sample t tests were used for comparison between variables. Values are presented as mean ± standard deviation. Statistical significance was assumed for p values of less than 0.05.

Results and Comment

All patients underwent the initial operation without complications. Patients with a silicone pouch undergoing wire retrieval and insertion of the AICD generator at a later time spent significantly less time in the operating room than those who did not have it (140.0 ± 10.8 versus 120.0 ± 5.0 min; $p < 0.05$). Of the patients without the silicone pouch, fat necrosis (sterile cultures) of the subcutaneous pocket developed in 1. A pocket infection with *Staphylococcus epidermidis* developed in 1 other patient and resolved after 5 days treatment with antibiotics. In 1 patient with the silicone pouch a sterile seroma developed and was evacuated at the time of generator implantation.

In conclusion, the use of a silicone pouch to protect AICD leads in patients who do not require implantation of the AICD generator at the time of initial operation represents a good alternative technique. We have found that the overall operative time for retrieval of patch lead wires and insertion of the AICD generator is reduced significantly. This technique is a safe and efficient method to quickly find the leads and to avoid the postoperative consolidation of fibrous tissue at the subcutaneous pocket level. This in turn allows implantation of the AICD generator to become a simple and straightforward procedure with good long-term results and a reduction in related morbidity.

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Single Venous Cannulation Through the Right Atrium for Venous Return in Valve Operations

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We present a method of single venous cannulation through the right atrium that can be used for operation on the mitral valve.

(Ann Thorac Surg 1991;51:506–7)

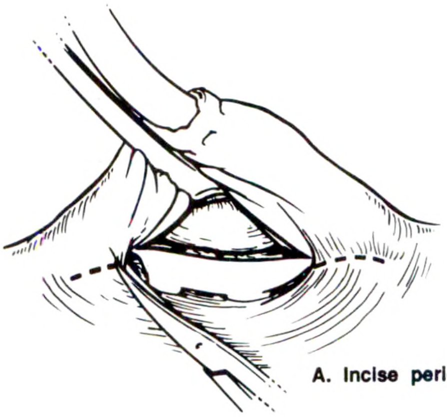
Most cardiac surgeons, as a routine, cannulate both the superior vena cava (SVC) and the inferior vena cava in all patients in whom a mitral operation is contemplated. It has been our experience that a single venous cannula through the right atrium with a standard venoatrial cannula provides an excellent venous return, not only for aortic, but also for mitral valve procedures.

Method

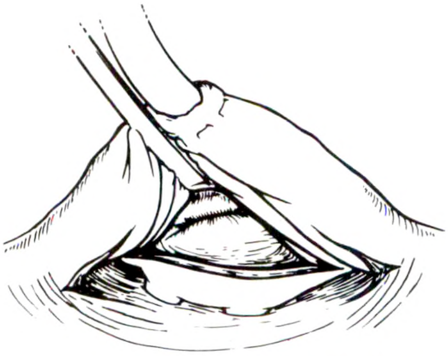
A standard midsternotomy and aortic cannulation are performed. Unless the tricuspid valve is intended to be exposed, a venoatrial cannula (a two-stage single venous cannula) (Sarns Inc, Ann Arbor, MI) is introduced through the right atrial appendage and directed into the inferior vena cava. The cannula is held with a pursestring and a tourniquet that, once tightened, is tied onto the cannula to reduce the number of instruments in the operative field. A tape surrounding the atrial appendage at the point of the entrance of the cannula is tied with a single knot so that it can be easily removed without injury to the atrial wall by pulling on it at the time of decannulation. Cardiopulmonary bypass is initiated in a manner similar to that of any coronary bypass operation. Where the aortic valve is going to be exposed the venous return line is directed downward, parallel to the right blade of the sternal retractor. When a left atriotomy is planned the venous return line is displaced upward over the ascending aorta so that it lies in a smooth curve toward the neck and to the left of the patient. The assistant pulls the right atrium and cannula toward the left. The pericardial reflection on the SVC is sectioned, and by blunt dissection the lateral aspect of the SVC is dissected free (Fig 1). This maneuver allows the superior extension of the left atriotomy and it avoids kinking of the SVC when the retractors are placed in the left atrium in patients in whom the SVC is cannulated through the right atrial appendage. We normally use two hand-held Deaver retractors, which in our opinion give a better exposure of the mitral valve. When a fixed retractor is used care must be taken to avoid total obstruction of the SVC with its upper edge.

Comment

The efficiency of single venoatrial cannulation through the right atrium has achieved universal acceptance for coronary artery bypass operations. A large number of surgeons also use it for single aortic valve operations, given its simplicity and excellent venous return. We started



A. Incise pericardial reflections



B. Atriotomy incision extended

Fig 1. Extended left atriotomy after section of the pericardial reflections over the superior and inferior venae cavae. The interatrial septum and right atrium with venoatrial cannula are retracted anteromedially. (Reproduced from J Cardiac Surg 1990;5:167, by permission of the Futura Publishing Co.)

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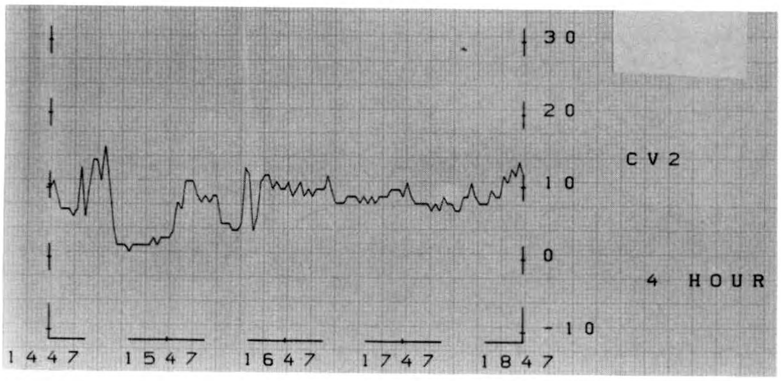

Fig 2. Continuous pressure monitoring of the superior vena cava, showing no evidence of venous stagnation. (x axis = time; y axis = pressure in mm Hg.)

using this technique for mitral operations about 5 years ago and were impressed by its simplicity, rapidity of insertion, and excellent venous return. During the procedure the SVC has to be observed carefully for evidence of venous stagnation and, if necessary, the atrial retractor has to be readjusted. Care must be taken to avoid the cannula unexpectedly slipping into the inferior vena cava, causing partial obstruction of the venous return through the atrial port. Continuous monitoring of the pressure in the SVC showed no venous stagnation (Fig 2). No upper body edema or neurological deficit was encountered, and therefore this technique has been the standard cannulation method in more than 400 cases performed since then.

We wish to thank Alison Silkstone for her secretarial assistance.

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Autogenous Atrial Tunnel for Direct Cavopulmonary Connection in Infants and Small Children

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A technique is described for construction of an autogenous right atrial tunnel for direct cavopulmonary connection in infants and small children requiring Fontan operation. Advantages, in this subset of patients, of this method over others previously described using prosthetic or growth-limited materials are suggested.

(Ann Thorac Surg 1991;51:508–10)

Theoretical and practical advantages have been proposed for creation of the Fontan circulation using direct cavopulmonary connection [1–4]. Intraatrial channeling of inferior vena caval return has been described using pericardial baffles, Dacron or Gore-Tex tube grafts, or baffles cut from tube grafts [1–4]. To avoid the use of prosthetic or growth-restricted material in the infant or small child requiring direct cavopulmonary connection we have recently used a modification of the Senning technique in which a flap of right atrial free wall is used to create a circumferential atrial tunnel from inferior vena cava to superior vena cava. Described are 2 cases in which we have used this technique.

Technique

Individual caval cannulation was carried out using angled metal cannulas. A right atrial free wall flap based on the sulcus terminalis was cut to size from eustachian valve inferiorly to just caudal of the superior vena cava superiorly. Where necessary, the atrial septal defect was enlarged anteriorly and superiorly. The right atrial tunnel was then constructed by suturing the atrial flap around the entrance of the inferior vena cava, using eustachian valve where present, and similarly around the origin of the superior vena cava extending somewhat medially to allow an enlarging incision (if necessary) into the right atrial wall for superior vena caval connection. The flap was then sewn along the atrial septum, posterior to atrial septal defect, to complete the tunnel (Fig 1). Coronary sinus was left in the low-pressure pulmonary venous chamber. Superior caval connections were then carried out as dictated by the pulmonary artery anatomy. The anterior wall of the right atrium was brought down and anastomosed to the outer wall of the atrial tunnel to reconstruct the pulmonary venous chamber or the atrial wall defect was filled with a suitable pericardial patch.

Case Reports

Patient 1

An 11-month-old, 4.9-kg infant had single ventricle, aorta arising from rudimentary left-sided chamber, severely restrictive ventricular septal defect (100-mm Hg gradient) and severe subpulmonic stenosis. At operation the main pulmonary artery was transected, subpulmonic obstruction resected, and a double outlet created (Damus-Kaye-Stansel). The inferior vena caval blood was redirected to the transected, enlarged superior vena cava using the described intraatrial tunnel, and the caudal superior vena cava was anastamosed to the transected main pulmonary artery. The cephalad transected superior vena cava was connected end-to-end to the transected distal right pulmonary artery. Because of prolonged periods of complete heart block preoperatively, permanent ventricular pacing electrodes were left epicardially and a generator was placed postoperatively. Postoperative catheterization showed no obstruction of the inferior vena cava to left pulmonary artery blood flow (Fig 2). Twenty-four months postoperatively the atrial tunnel remains widely patent (Fig 3A).

Patient 2

A 20-month-old, 8-kg female infant with double-inlet single ventricle and L-malposition of the great vessels with aorta arising from a rudimentary left-sided right ventricle, a nonrestrictive ventricular septal defect, and moderate pulmonic stenosis was seen with failure to thrive and poorly controlled heart failure. At cardiac catheterization the pulmonary to systemic shunt ratio was 4:1, mean pulmonary artery pressure was 20 mm Hg, and the pulmonary to systemic resistance ratio was less than 0.1.

An intraatrial tunnel for inferior vena caval return was constructed as described. Direct cavopulmonary connection was established by anastomosis of caudal transected superior vena cava to the right pulmonary artery at the junction with the main pulmonary artery and cephalad superior vena cava to the superior aspect of the right pulmonary artery.

The child was discharged home, but returned 2 weeks later with ascites and pleural effusions. Repeated echocar-

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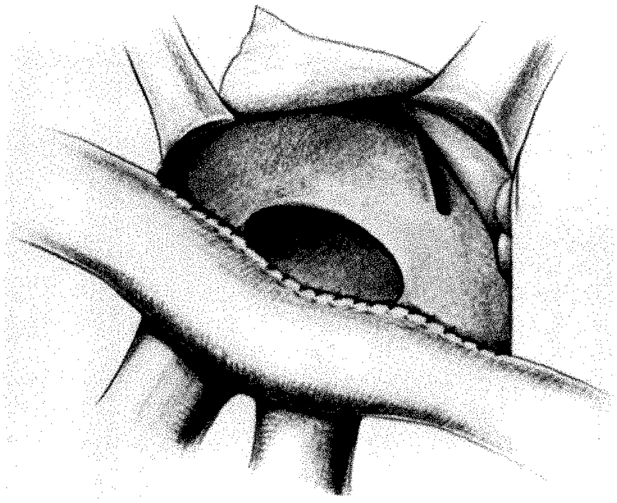

Fig 1. Right atrial free wall flap channels inferior vena caval blood to superior vena cava. Atrial septal defect provides inflow to right atrioventricular valve.

diographic evaluation revealed no right-sided obstruction (Fig 3B). She died 2 months postoperatively of *Candida* sepsis. She remained in normal sinus rhythm throughout her postoperative course.

Comment

Advantages of total cavopulmonary connection for the Fontan procedure have been described. Reduced loss of energy by direct channeling of blood to pulmonary arteries has been suggested [1]. Advantages of maintaining low pressure in the coronary sinus have been reported [5]. There are cases of complex congenital cardiac anatomy in which intraatrial baffling or channeling of inferior vena caval blood to the superior vena cava is certainly advantageous for creation of the Fontan circulation. These include cases, predominantly of the single-ventricle complex type, where the right atrioventricular valve provides ventricular inflow (eg, mitral atresia) or where indeterminate nodal or conduction abnormalities make uncomplicated patch closure of the right atrioventricular valve difficult. Distortion of pulmonary anatomy by previous

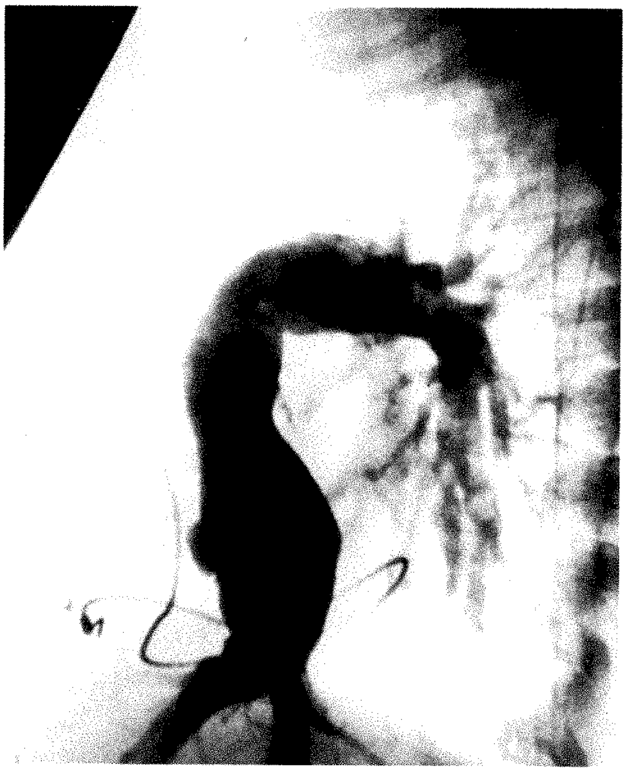

Fig 2. Postoperative inferior venacavogram of patient 1.

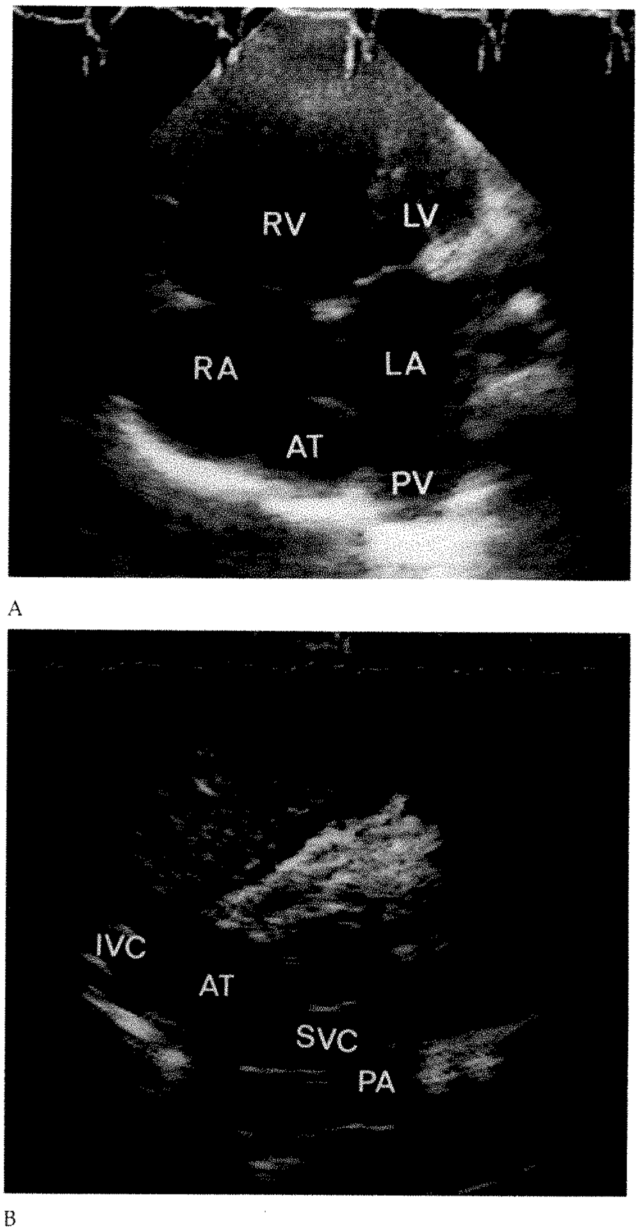

Fig 3. (A) Echocardiogram of patient 1, 24 months postoperatively. (B) Echocardiogram of patient 2, 1 month postoperatively. (AT = atrial tunnel; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; PA = pulmonary artery; PV = pulmonary veins; RA = right atrium; RV = right ventricle; SVC = superior vena cava.)

shunts or abnormal growth patterns also may be best managed by cavopulmonary connection, as may multiple venous-atrial connections (eg, atrial isomerism) [2, 4].

Many techniques of construction of intraatrial tunneling of inferior vena caval blood to the superior vena cava have been described [1–4]. My colleagues and I believe that in the infant or small child a complete atrial tunnel has advantages over other methods. A similar technique used in the Senning procedure for transposition of the great arteries resulted in less obstruction when compared with methods using pericardium or Dacron baffles [6]. The use of complete intraatrial tube grafts is limited in infants by conduit size. Partial prosthetic tunnels are thought to grow through an increase in posterior wall size. That growth over time, however, remains to be evaluated, and recent experience has shown an increased rate of pulmonary pathway obstruction when prosthetic material has been employed in other techniques for Fontan connection [7]. Long-term follow-up on growth of the autogenous atrial channel has not been done but, using the Senning procedure experience, growth of the tunnel can be expected.

The technique presented here provides a method of direct cavopulmonary connection in infants and small children that avoids the use of prosthetic or growth-limited materials.

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Jatene's Arterial Repair for Transposition of the Great Vessels

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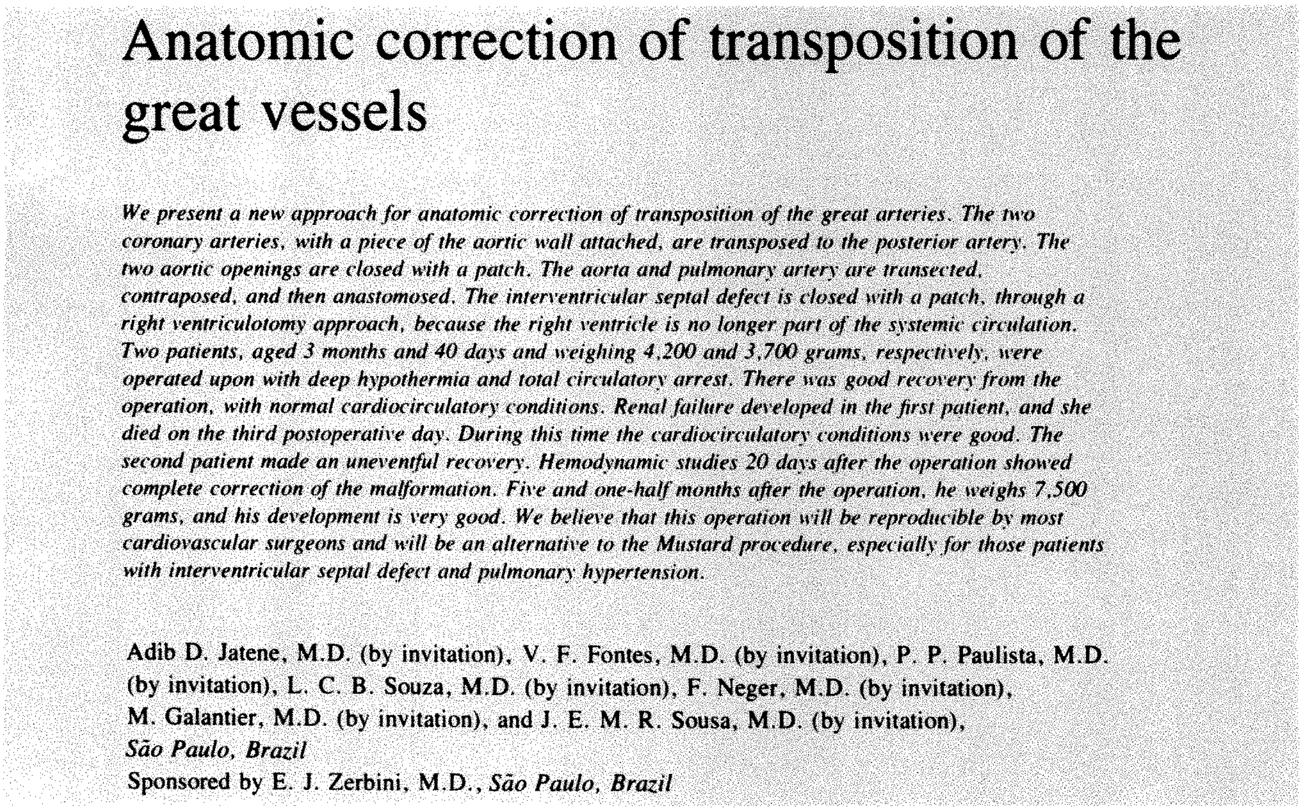
In 1975, Adib Jatene demonstrated the clinical feasibility of an arterial repair for transposition of the great vessels. This repair consisted of removing the left and right coronary arteries and reanastomosing them to the adjacent pulmonary artery, which was to become the neoaorta, and by transecting and transposing the aorta and main pulmonary artery. This repair varied from previous "arterial switch" procedures in that the aorta and pulmonary artery are divided distal from the aortic and pulmonary valves, and the coronary arteries are removed with a button of aortic wall facilitating the anastomosis to the neoaorta. Initially limited to patients with transposition and a large ventricular septal defect "preparing" the left ventricle, the indications for the arterial repair have been expanded to include neonates with simple transposition and other more complex lesions. Early results suggest that this anatomical and physiological approach will eliminate many of the complications associated with the physiological atrial repairs.

(Ann Thorac Surg 1991;51:511–4)



Anatomic correction of transposition of the great vessels

We present a new approach for anatomic correction of transposition of the great arteries. The two coronary arteries, with a piece of the aortic wall attached, are transposed to the posterior artery. The two aortic openings are closed with a patch. The aorta and pulmonary artery are transected, contraposed, and then anastomosed. The interventricular septal defect is closed with a patch, through a right ventriculotomy approach, because the right ventricle is no longer part of the systemic circulation. Two patients, aged 3 months and 40 days and weighing 4,200 and 3,700 grams, respectively, were operated upon with deep hypothermia and total circulatory arrest. There was good recovery from the operation, with normal cardiocirculatory conditions. Renal failure developed in the first patient, and she died on the third postoperative day. During this time the cardiocirculatory conditions were good. The second patient made an uneventful recovery. Hemodynamic studies 20 days after the operation showed complete correction of the malformation. Five and one-half months after the operation, he weighs 7,500 grams, and his development is very good. We believe that this operation will be reproducible by most cardiovascular surgeons and will be an alternative to the Mustard procedure, especially for those patients with interventricular septal defect and pulmonary hypertension.

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The arterial correction of transposition of the great arteries became a reality with Adib Jatene's repair reported in 1975 [1] and 1976 [2]. As is often the case, this anatomical as well as physiological repair is striking in its elegant simplicity and straightforward solution, which had eluded earlier surgical investigators.

Historical Considerations

Bailey and associates [3] attempted transposing the great vessels employing circulatory arrest in 1953. With no

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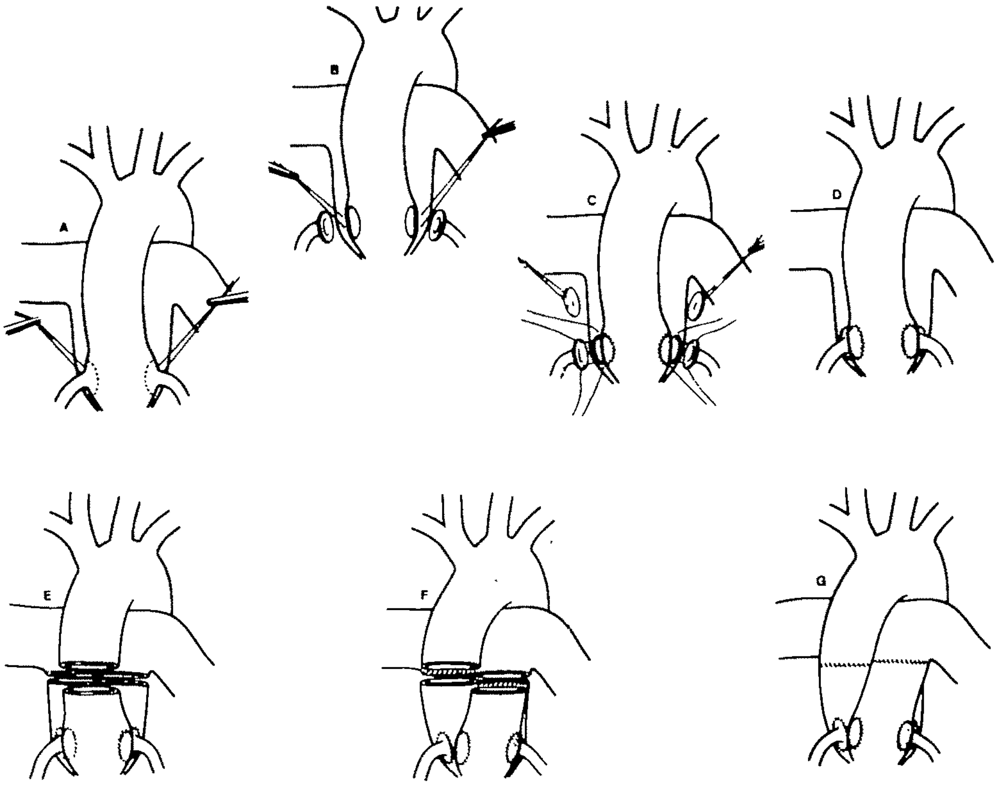

Fig 1. Jatene's original illustration demonstrating the anatomical correction employing aortic buttons to facilitate reanastomosis of the coronary arteries to the neoaorta. (Reproduced from Jatene AD, Fontes VF, Paulista PP, et al. Anatomic correction of transposition of the great vessels. J Thorac Cardiovasc Surg 1976;72:364–70, with permission of Mosby-Year Book, Inc.)

survivors, and concern with the neopulmonary position of the coronary arteries, the investigators abandoned the procedure.

In 1954, Mustard and co-workers [4] attempted an arterial repair in 7 patients. The repair incorporated the left coronary artery but not the right coronary artery in the neoaorta. Uniform failure was secondary to coronary distribution forcing abandonment of the procedure, low cardiac output, and problems associated with early cardiopulmonary bypass employing a monkey-lung oxygenator. Mustard's later attempts centered on the arterial repair.

The next year, Senning [5] attempted an arterial switch procedure in which the aorta and pulmonary artery were transected just above the aortic and pulmonary valves, respectively, and transposed, moving both the coronary arteries en bloc with the aorta. Having no clinical success with this procedure, Senning abandoned it in 1957 for the arterial repair bearing his name.

Other suggested arterial repairs [6–9] have been offered either theoretically or in animal models. The overwhelming dilemmas facing these earlier investigators have been the coronary arteries and the physiologically unprepared left ventricle in simple transposition, as the pulmonary resistance and hence pressure dropped after birth.

Jatene's Arterial Repair

After these early attempts at arterial repair for transposition of the great arteries, most efforts focused upon atrial repairs which enjoyed greater success. In 1975 in a preliminary report [1] and in 1976 in the United States [2], Jatene and associates reported their clinical experience with an arterial repair. Although the first attempt was unsuccessful secondary to renal failure in the early postoperative period, the second attempt on a 40-day-old, 3,700-g infant with transposition and a large ventricular septal defect was successful. The repair (Fig 1), employing hypothermic circulatory arrest, consisted of removing the left and right coronary arteries and reanastomosing them to the adjacent pulmonary artery, which was to become the neoaorta, and transecting and transposing the aorta and main pulmonary artery. The ventricular septal defect was closed with a Dacron patch through a right ventriculotomy.

This repair varied from previous procedures in two ways. First, the aorta and pulmonary artery are divided distally, far from the aortic and pulmonary valves, thus avoiding coronary artery and valve distortion. Second, the coronary arteries are removed with a button of aortic wall facilitating the anastomosis to the neoaorta, and minimizing both the early and late risk of ostial stenosis.

The Role of the Arterial Repair Today

After the early experience of Jatene and others, attention was turned to modifications of the surgical technique and expanding the indications of the arterial repair. Although Jatene's repair initially used no graft material in the aortic or pulmonary anastomosis, it became apparent that the pulmonary anastomosis was often under tension, inducing obstruction. Conduits and graft material were used to prevent this but raised concerns of long-term results [10]. Lecompte and associates [11], in 1981, introduced the maneuver of placing the aorta behind the dissected pulmonary artery, thus reducing tension and eliminating the need for a prosthetic graft. Variations of the coronary artery anatomy including a single coronary os were initially contraindications to the arterial switch repair. Modifications of the repair have been devised so that all but a very few coronary patterns can be successfully repaired [12–14].

Jatene noted early in his experience that the unprepared left ventricle was not capable of performing under systemic pressure conditions after an anatomical repair [15]. The arterial switch procedure was thus limited to anatomical variations where the left ventricular pressure was already near or equal to systemic pressure such as in patients with large ventricular septal defects or repairable pulmonary stenosis. Yacoub and colleagues [16] introduced the two-stage repair for simple transposition in which the pulmonary artery is banded in the first stage to prepare the left ventricle and permit an arterial switch as a second procedure. The concept of neonatal arterial repair [14, 17] has expanded the criteria to nearly all patients with simple transposition. The repair is performed within the first few weeks of life while the left ventricle remains prepared by the physiological pulmonary hypertension of the newborn in transition from fetal to mature pulmonary hemodynamics.

Recent experience in a large cooperative study [18] has demonstrated that the arterial repair in the neonate can be performed by an experienced surgical team with a low mortality rate. Intermediate-term results are promising despite some late complications such as valvar insufficiency and pulmonary stenosis in a small number of children. It is to be hoped that the late complications of arterial repairs, including arrhythmias, baffle obstruction, tricuspid regurgitation, and right ventricular dysfunction, can be avoided with the Jatene repair and its modifications.

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Editor's Note

We asked Dr Jatene to comment on Dr Dunn's article.

Invited Commentary

I feel honored by Dr Dunn, who wrote this paper, and by Dr Ferguson for asking me to add a comment.

It is not easy for a South American surgeon to make new contributions, because most of us work under difficult conditions, which preclude investigations and research. However, I had the good fortune of being trained at the University Hospital by Professor Zerbini, with whom I worked from 1951, when I was still a medical student, to 1962, when I left to start my own group. Even after leaving I still remained in close contact with him. Together with Luiz Décourt, Dante Pazzanese, and a number of other cardiologists, Zerbini contributed to the creation of two strong institutions in the state of São Paulo: the Instituto do Coracão of the University Hospital of the School of Medicine and the Instituto Dante Pazzanese de Cardiologia of the State Health Department, where I worked from 1962 to 1983, when I returned to the University to replace Prof Zerbini, who had just retired.

The two institutions accumulated a large clinical experience in the different areas of the specialty, which today represents more than 80,000 heart operations, almost 40% being coronary revascularization. A very large number of surgeons and cardiologists trained in the institutions are now active all over the country. Both institutions pioneered investigations in the fields of bioengineering and clinical research at a high-priority level. Today such activities have become established as essential routine for the best centers in the country.

From the very start, we worked in congenital as well as in acquired disease, treating adults, children, and infants. Our first correction of a tetralogy of Fallot in an infant was successfully performed in 1960, in a 3-month-old girl weighing 4 kg. She is now 30 years old and the mother of two children, and leads an entirely normal life.

The accumulated experience in coronary surgery—which we started in 1968 and which already included more than 2,000 cases in 1975—associated with the study of a large number of normal hearts as well as pathological specimens with transposition of the great arteries finally convinced us that the arterial repair of transposition of the great arteries was possible.

During the Second Symposium of the Henry Ford Hospital, in 1975, I presented, in a comment, 2 patients with one death. Subsequently, at the 1976 meeting of the American Association for Thoracic Surgery, to these 2 patients I added 5 more, all of whom died.

I firmly believe that the discussion of these unsuccessful cases helped to avoid excessive premature enthusiasm and ensured the progressive and careful acceptance of the method, which is currently performed all over the world with very good results, as are being demonstrated by the cooperative study in neonates run by the Heart Surgeon Congenital Society.

Our present experience runs to 151 operated patients, the vast majority associated with ventricular septal defect or patent ductus arteriosus. This experience is not larger because only recently we began to consider our care infrastructure as capable of managing neonates with elective indications at an acceptable level of safety.

I am especially gratified when I receive in my office teenaged patients who had been treated in their first months of life and who now enjoy a normal life with no concerns about complications. The only major problem we have encountered is pulmonary stenosis, which we detected in 5 patients. Two underwent reoperation 5 years after the original correction, with one death. Two others were submitted to balloon dilation with good results.

Other problems, such as valve insufficiency, late coronary occlusion, proximal aortic aneurysms, or left ventricular problems are now known to be very infrequent. Taken jointly, these findings have been largely responsible for the universal acceptance of the technique.

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Fistulas Between the Aorta and Tracheobronchial Tree

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Aortobronchial fistula is a rare condition that is invariably fatal if not diagnosed and surgically treated. With appropriate surgical intervention, survival rates greater than 70% can be achieved. A review of the literature and an illustrative case report are presented. A total of 63 fistulas in 62 patients have been described. The case we present is unusual in the use of serratus anterior muscle for repair of the fistula. Eighty-seven percent of the cases documented in the literature were associated with an aneurysm of the thoracic aorta. Eighty-six percent of the fistulas were between the descending aorta and left bronchopulmonary tree. More than 95% of patients experienced at least a single episode of hemoptysis, and massive hemoptysis occurred in more than half of the reported cases. A correct preoperative diagnosis was made in only 54% of cases. Plain chest radiographs definitively demonstrated an aneurysm in only 16%. The computed tomographic scan was the most rewarding test, identifying an aneurysm in 11 of 12 patients and the fistula in 50% of them. Surgical repair resulted in a 76% survival rate.

(Ann Thorac Surg 1991;51:515–9)

The occurrence of a fistulous communication between the thoracic aorta and tracheobronchial tree is rare. Review of the literature revealed 63 cases (62 patients) in addition to the one documented here [1–44]. Most commonly seen in patients with thoracic aortic aneurysms, this condition is highly lethal if undiagnosed. Its lethality mandates a high index of suspicion in any patient with massive hemoptysis. Early diagnosis offers the benefit of complete recovery by means of a surgical lifesaving procedure. The illustrative case report highlights the application of newer diagnostic and therapeutic modalities such as computed tomographic scanning and the use of muscle transposition to prevent infection in the presence of a vascular prosthesis.

Case Report

An 86-year-old man with a history of chronic obstructive lung disease and reflux esophagitis was seen with a 4-month history of intermittent hemoptysis. He had had a similar problem on one occasion 4 years previously. Chest roentgenogram showed a mass in the lower aspect of the left chest adjacent to the posterior mediastinum. At bronchoscopy, extrinsic compression of and bleeding from the left lower lobe orifice were noted. The patient had a respiratory arrest during the procedure but was successfully resuscitated. After recovery, it was presumed that he had carcinoma, and he underwent mediastinoscopy. The results were negative. Subsequently, at thoracotomy, an aneurysm of the descending aorta was identified with dense adherence to the posterior surface of the left lower lobe. The thoracotomy was closed, and the patient was transferred to our institution for definitive management.

A computed tomographic scan (Fig 1) and aortogram were made (Fig 2). It was apparent that the situation was by then compounded by pneumonia in the left lower lobe. Sputum cultures grew *Staphylococcus aureus* and *Escherichia coli*. Concerns were raised about placing a vascular prosthesis in an infected field, and the patient was therefore initially treated with broad-spectrum antibiotics. Approximately 24 hours later, he had another bout of massive hemoptysis. After resuscitation and stabilization, he was taken to the operating room.

Left thoracotomy was performed through the previously opened fifth intercostal space. Proximal control of the aneurysm was obtained. The eighth intercostal space was used to obtain distal control of the aorta just above the diaphragm. The left femoral artery and vein were cannulated, 400 U/kg of heparin sodium was given, and the patient was placed on partial cardiopulmonary bypass. The aorta was clamped, and the aneurysm was opened, leaving the anterior aspect attached to the left lower lobe. Thrombus was removed, and a 22-mm Dacron graft was sewn in place with continuous suture. The patient was weaned from cardiopulmonary bypass.

The latissimus dorsi muscle had been divided during the first thoracotomy and was therefore not suitable for intrathoracic transposition. The serratus anterior muscle was detached from its multiple insertions in the ribs, and an 8-cm segment of fourth rib was resected in the midaxillary line. The mobilized muscle was passed into the chest cavity and interposed between the graft and the aortic wall adherent to the lung. There was sufficient muscle to cover the entire graft. Intraoperative cultures of the aortic wall grew *Staphylococcus epidermidis*, for which the patient received antibiotics for the next 6 months.

The postoperative course was protracted, and the patient was not discharged from the hospital until 47 days

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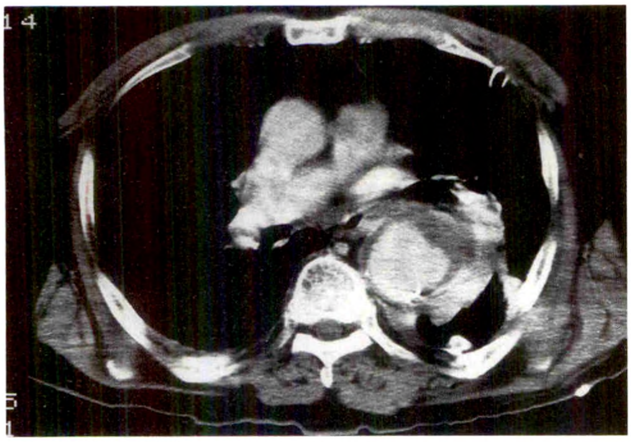

Fig 1. Computed tomographic scan of the chest shows thrombus in the aneurysm with adherence to the left bronchus.

after operation. Chest roentgenogram made just before discharge showed evidence of the transposition (Fig 3) but was otherwise normal. It has now been more than 2 years since the operation, and the patient remains well with no evidence of graft infection.

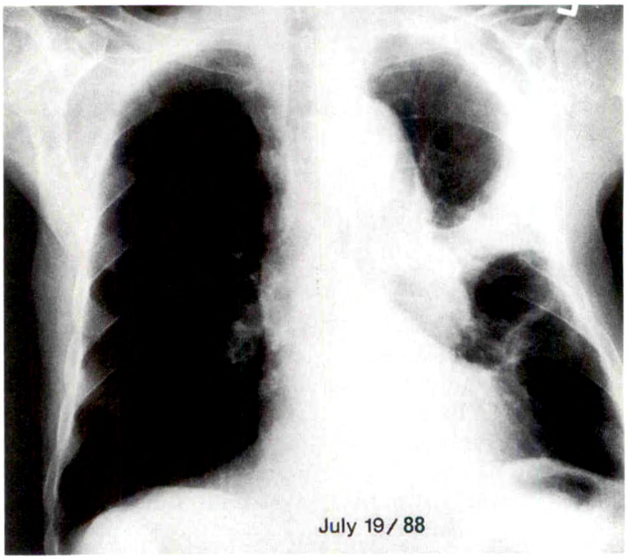

Fig 3. Chest roentgenogram made 2 months after repair of the aneurysm. The serratus anterior muscle has been transposed into the thorax and wrapped around the prosthesis, thus isolating the graft from the aneurysm wall, which was left adherent to the lung.

Historical Perspective

In 1934 in the first reported series of aortic aneurysm, Keefer and Mallory [1] documented six autopsy cases where a fistula existed between the thoracic aorta and tracheobronchial tree. All were associated with an aneurysm of the thoracic aorta, only one of which was syphilitic in nature. Another patient also had pulmonary tuberculosis, which was thought to be incidental. In 1947, Jones [2] reported the first successful surgical repair of an aortobronchial fistula. The patient was an 11-year-old girl with recurrent hemoptysis who had undergone surgical ligation of a patent ductus arteriosus 2 years previously. Thoracic exploration revealed dense adherence of the left upper lobe to the site of the previous patent ductus arteriosus ligation on the aorta. The fistula was repaired by primary closure of the aortic opening with silk and obliteration of the pulmonary opening with catgut interposed with mediastinal pleura. The patient made an uneventful recovery and was reported to be well 3 years later. In 1959, DeProphetis and associates [3] repaired an aortobronchial fistula, which had resulted from rupture of a thoracic aortic aneurysm. The patient died 26 days later secondary to a recurrent rupture.

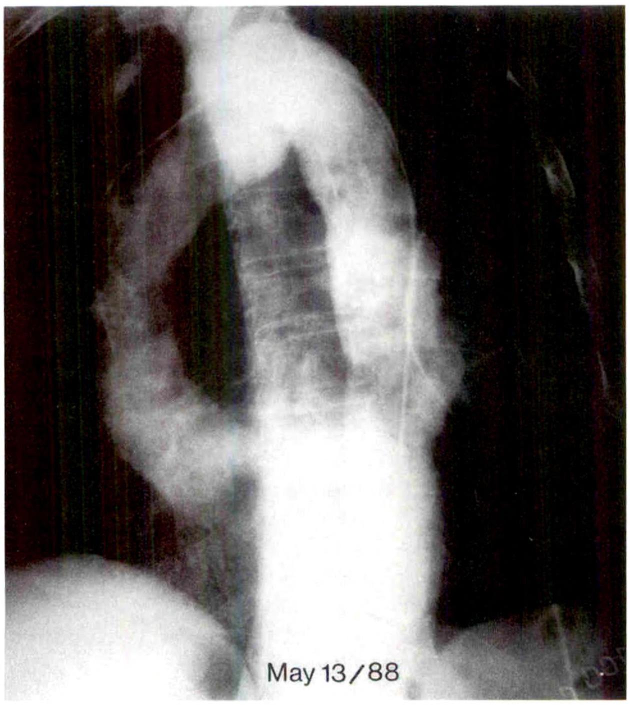

Fig 2. Aortogram shows a fusiform aneurysm of the mid-descending aorta with evidence of thrombus in its wall.

Pathophysiology

The majority (87%) of reported cases of aortobronchial fistula involve an aneurysm of the thoracic aorta. Expansion of the aneurysm causes tracheobronchial compression [45–48], and adherence will occur owing to chronic inflammation secondary to infection in the lung, foreign body reaction, or pressure necrosis. Rupture can be confined to a mediastinal structure such as the tracheobronchial tree or can be free into the pleural space.

Before 1960, mycotic aneurysms caused by tuberculosis, syphilis, and other organisms were the leading cause of aortobronchial fistula. In the decades following, atherosclerosis became a more common causal factor, and currently the most common causes are postsurgical and atherosclerotic aneurysms. Since 1980, 75% of reported cases have occurred after a previous thoracic aortic vascular procedure with the time from operation to presentation ranging from 4 months [2] to 17 years [39]. The presence of a foreign body, such as the suture material or the prosthetic graft itself, can elicit an inflammatory response resulting in pathological fixation of tissue and leading to fistula formation. With compression of the tracheobronchial tree, there often is associated pulmonary collapse and infection, which enhances the pathological process. Theories to explain fistula formation therefore include either local infection or mechanical stress causing formation of a pseudoaneurysm, though these are by no means mutually exclusive.

Nine fistulas have been reported after repair of a congenital abnormality, three patent ductus arteriosus and six coarctation repairs. Aortobronchial fistulas have also resulted from erosion by a chest tube, spinal fixation device, azygos node broncholith, and rib fragment [11–13, 49].

The site of the fistula is determined by the anatomical structure adjacent to the aneurysm [50]. Thoracic aneurysms occur most frequently in the descending aorta [46], and therefore it is not surprising that the majority of reported cases (54/59, 92%) involve the descending aorta and left bronchial tree. Of the left-sided aortopulmonary fistulas, the site of perforation was not specified in seven cases and occurred into the left main bronchus in six [1, 10, 15–17]. Of the remainder, half involved the pulmonary parenchyma of the upper lobe and half, the lower lobe. There were three cases of fistulas occurring between the ascending aorta and right bronchopulmonary tree, including a postmortem description of an aortoesophagobronchial fistula resulting from miliary tuberculosis [1, 19, 20]. In the presence of an aortic prosthesis, the fistula usually occurred at one of the anastomotic sites. The site was documented in 12 of 16 cases and involved the proximal anastomosis in nine cases and the distal anastomosis in two. In a single instance, the aortic leak had occurred through the body of the Dacron prosthesis [21].

Epidemiology

Bickerstaff and co-workers [51] reported an annual incidence of thoracic aortic aneurysm of 5.3 per 100,000 population with rupture occurring in 74% within 5 years if left untreated. An identified subpopulation at particularly high risk is the group of patients who have undergone previous thoracic aortic operations. The incidence of the development of thoracic aortic aneurysms is similar for men and women, but more than two thirds of the documented cases of aortobronchial fistula have occurred in male patients. Aortobronchial fistula can develop in any decade, but the incidence generally increases with age. Five cases have been reported in children, the youngest being a 5-year-old boy who had correction of patent ductus arteriosus and coarctation as a neonate [10]. When he was 5 months old, he required an aortic prosthesis for occlusion. At the age of 5 years, he had false aneurysm formation at the distal aortic anastomosis.

Clinical Features

The clinical course of aortobronchial fistula is characterized by recurrent hemoptysis with virtually all patients experiencing at least one episode. Massive hemoptysis, defined as the expectoration of more than 400 mL of blood in 24 hours [22], is reported to occur in more than half of the patients and is often the terminal event. The intermittent nature of the hemoptysis is explained by the thrombogenicity of the pulmonary parenchyma. When the fistula is first established, a small amount of blood will be expectorated. The hemoptysis will stop after clot formation in the fistula. When the clot lyses or becomes dislodged, more hemoptysis ensues. This process is repeated until the fistulous opening and the hemorrhage become large enough to cause exsanguination [23]. In 11 patients, massive hemoptysis was associated with cardiorespiratory arrest. Eight of these patients survived after resuscitation and successful surgical repair [3, 10, 14, 19, 24–26]. Hemoptysis of this degree is rare in primary disease of the lung and must therefore be presumed to be due to aortobronchial fistula. Exceptions include chronic pulmonary tuberculosis, a terminal event in carcinoma of the lung, and chest trauma [27, 28].

Dyspnea, cough, and sputum are also frequent symptoms resulting from airway compression by the expanding mass. The duration of pulmonary symptoms, both obstructive symptoms and hemoptysis, has been as long as 4 years [12].

Diagnostic Modalities

Aortobronchial fistula should be suspected in every patient with a mediastinal mass and recurrent hemoptysis. The mass can be obscured by other mediastinal structures or secondary pulmonary changes [16]. Graeber and associates [23] stated that plain roentgenograms of the chest are the most helpful diagnostic study because they denote abnormalities in the lung adjacent to the aneurysm. However, an aneurysm was prospectively and definitively diagnosed in only seven of 44 cases (16%) when chest roentgenographic findings were noted. In more than half the cases, the findings were nonspecific, consisting of pulmonary infiltrates. In only three of 44 instances was the chest roentgenogram interpreted as normal [4, 6, 29]. Chest radiography therefore has its limitations, and additional investigations to delineate the cause of hemoptysis are now more commonly also used.

Bronchoscopy is the best means of identifying the source of the bleeding [29]. However, it is unlikely to be helpful and could, in fact, be hazardous and should be avoided in suspected cases of aortobronchial fistula. Many catastrophic events have occurred with bronchoscopy, with and without attempted biopsy, including dislodgment of clot precipitating hemorrhage and respiratory arrest [3, 10, 24, 25, 30, 37].

Angiography may be helpful in demonstrating an aneurysm. It has not been reported to precipitate hemorrhage, although the possibility exists. It should be performed only under circumstances that allow immediate definitive surgical intervention should it be required.

Angiography was performed in 23 patients with demonstration of an aneurysm in 18 (78%), suspicion of aneurysm in 2, and ruptured aorta in a patient with traumatic fistula. In the 2 remaining patients, the angiogram was reported as normal [32, 38]. The aortogram does not usually demonstrate the clot-filled fistula, although it was seen in 4 patients [6, 9, 32, 33].

Computed tomography has been used since the late 1970s in the investigation of aortic pathology. It is the primary method used to differentiate a mediastinal or paramediastinal lung mass from a saccular aortic aneurysm. Computed tomography clearly demonstrates the relationship of the aortic aneurysm to the adjacent structures. An aortobronchopulmonary fistula is manifested as consolidation of the lung adjacent to the aneurysm [50]. An aneurysm was identified in 11 of 12 patients undergoing computed tomographic scanning, and in half of these the fistula itself was actually demonstrated. The role of magnetic resonance imaging in investigation of this lesion has not been defined. An aortobronchial fistula was demonstrated in a recent case report [31].

Management

The keystones to management include resuscitation, diagnosis, and definitive surgical intervention. Massive persistent bleeding can be controlled immediately by intubation of the contralateral (normal) bronchus by a single- or double-lumen endotracheal tube [32, 34, 35] or placement of a Fogarty catheter on the side of the hemorrhage [8]. If these measures fail, emergency thoracotomy may be lifesaving.

Surgical treatment of aortobronchial fistula consists of the repair of both the aortic and pulmonary defects. Circulation distal to the fistula has been maintained by partial or complete cardiopulmonary bypass, and repair has also been performed with aortic cross-clamping only. The aortic side of the fistula can be managed by patch closure, direct suture, or prosthetic graft, usually the latter. When a previously placed prosthesis is present, that graft should be removed because of the possibility of infection. In this situation, extraanatomical bypass has been performed in the past [7, 11, 36]. The bronchial side of the fistula can be managed with resection (wedge lobectomy, pneumonectomy) or simple closure.

The new graft and suture lines should be protected by interposing viable tissue. Most commonly, pleural or pericardial flaps have been used to cover suture lines. Others [23] have used intercostal muscle to buttress the bronchial closure. Wrapping with omental pedicles has been used successfully in the presence of chronic mediastinal or thoracic infection involving vascular prostheses [11, 52]. Extrathoracic skeletal muscles have been used extensively in the management of a variety of difficult problems in thoracic surgery [53]. The case described illustrates another useful application. Completely wrapping the graft with viable tissue has potential benefits in terms of clearing residual infection and should prevent recurrence of an aortobronchial fistula. The use of an extrathoracic skeletal muscle for this purpose rather than omentum avoids the added risk of opening a second body cavity in the presence of infection in patients who are already desperately ill.

Prognosis

Without surgical intervention, aortobronchial fistula is uniformly fatal. Of the 34 reported patients in whom surgical repair was attempted, successful repair was achieved in 26 (76%). Five deaths occurred intraoperatively, 4 secondary to uncontrollable hemorrhage and the other from pulmonary edema and heart failure. Three deaths occurred within 1 month postoperatively. One patient died after rupture of a second thoracic aortic aneurysm, and the other 2 patients died of pneumonia and overwhelming sepsis within 2 weeks after operation [28, 37]. Morbidity is substantial in this group of patients and commonly consists of pulmonary infection or neurological sequelae [19]. The majority of these patients require prolonged ventilation postoperatively, but with appropriate surgical treatment, most patients will make an excellent recovery.

Conclusion

A high index of suspicion is necessary to make the diagnosis of aortobronchopulmonary fistula. The diagnosis should be considered in any patient experiencing minor or major hemoptysis with either coexisting thoracic aortic aneurysm or a history of thoracic aortic operation. The computed tomographic scan is the best single diagnostic modality available. Surgical cure with recovery can be achieved in most instances.

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Mediastinal Masses

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CORRESPONDENCE

Risk of Reintervention After Coarctation Repair

To the Editor:

We read with interest the article "Incidence and risk of reintervention after coarctation repair" by Kron and colleagues [1]. They advocate subclavian flap angioplasty (SFA) as a technique that leads to fewer reinterventions than resection and end-to-end anastomosis (RETE) in infants and young children. Kron and colleagues do not present, however, the incidence of hypoplasia of the isthmus or distal aortic arch, or both, in the patients in their series. In the discussion Dr Kron mentions that in the presence of "very long arch stenoses and hypoplastic arches,... we have done a couple of extended end-to-end anastomoses." The fact that the authors may favor an SFA repair in the presence of a well-developed isthmus and RETE in association with a hypoplastic isthmus, which is frequently accompanied by hypoplasia of the distal transverse aortic arch, may introduce bias against the RETE technique. It is well known that repair of coarctation superimposed on tubular narrowing of the isthmus or the distal transverse aortic arch, or both, is considerably more demanding than repair of a circumscribed paraductal coarctation [2]. Therefore, matching of the surgical technique to the underlying anatomical pattern of the isthmus and aortic arch may have negatively influenced the coarctation reintervention rate in the RETE group, as presented in this study.

A second bias against the RETE technique may have been intrinsic to the suture material as used in this study. Kron and colleagues do not mention the type and diameter of the suture that they use for the anastomosis. A relatively thick suture, such as 5-0 polypropylene (which was used by Dr Sade and coworkers [3], to whom Dr Kron refers) or polydioxanone may lead to increased damage of the internal elastic lamina of the aortic wall with subsequent increased risk of intimal hyperplasia, flow disturbances at the anastomotic site, and, ultimately, progressive narrowing of the residual lumen. Use of a strictly microvascular technique is especially important in the RETE technique because of the circumferential anastomosis. Therefore, we favor use of a 7-0 polypropylene or polydioxanone suture in RETE to minimize the risk of recurrent stenosis at the anastomotic site.

In the paraductal subtype of coarctation, in which the isthmus receives part of its flow in a retrograde fashion, proliferation of ductal tissue may occur at the downstream (facing the descending aorta) or upstream (facing the aortic arch) sides, or both, of the diaphragmatic ridge of the coarctation [4, 5]. In the preductal subtype ductal tissue is invariably found at the downstream side of the ridge [6, 7]. In both subtypes of coarctation a ductal tissue sling, representing the tail end of the original distal wall of the left sixth branchial arch, lines the periductal aorta from the entrance of the ductus arteriosus or the attachment of the ligamentum arteriosum toward and around the isthmic orifice. Taking these morphological data into consideration, it is virtually impossible to resect all ductal tissue in the SFA technique, which is considered an essential feature of this operation. At the best, a part of the prominent diaphragmatic ridge can be resected, leaving a rough surface with increased risk of retraction and restenosis. The circumferential lining of coarctogenetic ductal tissue, however, is left undisturbed, which may further narrow the lumen of the periductal aorta, as evidenced by a relatively high rate of early restenosis after SFA in early infancy [4, 8, 9].

In further reference to the aforementioned morphological findings, the isthmus must be completely resected in the RETE technique, as one can never be sure of the proximal extent of ductal tissue, especially in the paraductal subtype of coarctation. Incomplete resection of the isthmus, as depicted in Figure 1 of Dr Kron's article, may contribute to an increased rate of restenosis after RETE at a young age. An additional advantage of the RETE technique is that, in case of hypoplasia of the distal and even the proximal aortic arch, an extended resection can be performed [2, 4, 10]. The resultant extended anastomosis is limited only by the diameter of the aortic arch itself, thus allowing for maximal growth potential. In this context, extended RETE relieves hypoplasia of the aortic arch, whereas SFA may lead to further narrowing of this area [2].

A second drawback of SFA relates to the sacrifice of the left subclavian artery. Recently we documented long-term limitation in exercise with the left arm in patients who had undergone SFA in infancy [11]. We hypothesize that during explosive athletic exercise of the upper left limb, with an instantaneous steep increase of the metabolic demand, the underlying circulatory system may rapidly decompensate with ensuing symptoms of ischemia in the left upper limb.

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Reply

To the Editor:

I appreciate the opportunity to reply to the thoughtful letter by Drs van Son and Lacquet. Drs van Son and Lacquet clearly feel that end-to-end repair has substantial advantages as compared with subclavian flap angioplasty and present theoretical reasons for this difference. By and large, I have very little issue with their points and, to start off, would suggest that one should do what one does best. If, indeed, end-to-end anastomosis works best in your institution, then that is what you should do. However, there are some differences of opinion, and I would like to elaborate on these.

They make the point that subclavian flap angioplasty may do well at our institution if used in anatomically favorable situations. Obviously, this is true. The only way one will truly know which technique is best is to have a very large randomized trial of these techniques in patients with the same anatomy and age groups. It is doubtful that any single institution can do this. We did not state in our paper, as these authors suggest, whether or not the arches were hypoplastic. However, upon reviewing van Son and associates' paper [1], I cannot find this information in their paper either. I am not certain how important this is. There will be those patients who have hypoplastic arches that are truly coarctations, but many times a small arch will grow.

I also do not necessarily agree that the surgical technique, in terms of size of suture materials, is critically important to causing restenosis after end-to-end anastomosis. We use 6-0 polypropylene for end-to-end repairs and for most of our subclavian flap angioplasties. This is exactly what van Son and Lacquet have described using in their article, as well [1]. I cannot imagine, however, that carefully placed 5-0 polypropylene sutures really do make a difference. As long as some interrupted technique is used or a suture that will dissolve is used, I expect that stenosis would not be necessarily related to the technique per se. I am also not certain that leaving some periductal tissue predisposes to restenosis. In our hands, the reintervention rate for subclavian flap angioplasty in survivors of the procedure is still less than 10%, even in infancy. I doubt that this is statistically dissimilar from the results of van Son and Lacquet for end-to-end anastomosis in infancy. We find, however, that the mortality is low. The mortality for subclavian flap angioplasty is 5% and the majority of these procedures were done in infants, as young as less than a week of life. The procedure is technically easy to do and the risk is low. I do recognize that operative deaths are often related to the coexisting lesions, but even taking those into consideration, the mortality in our hands is quite low and I would expect would be significantly different from the mortality for end-to-end anastomosis quoted by van Son and Lacquet, which is 24% [1].

I do agree that the subclavian flap does require sacrifice of the left subclavian artery. I also reviewed van Son and associates' paper related to the hemodynamics of upper left limb after subclavian flap angioplasty [2]. We have followed our patients very closely from this standpoint using pulse volume recordings. Several years ago, we attempted to see whether or not subclavian flaps compared with end-to-end anastomosis, with or without sacrifice of the branches, might make a difference. We found no patients who truly had left arm claudication and cannot duplicate what van Son and colleagues very carefully showed in this latter reference. We just have not found that to be a clinical problem thus far.

In our institution, subclavian flap angioplasty has led to fewer interventions and is quite safe. We do believe that one should carefully review these techniques at each institution to determine the best procedure for these patients. I cannot imagine, however, that one will be able to presently reduce the risk of reintervention and mortality to 0. Therefore, careful follow-up and analysis of results are critical in the group of patients requiring coarctation repair.

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Membranotomy for Budd-Chiari Syndrome

To the Editor:

I wish to comment on the communication by Victor and associates [1] concerning membranous obstruction of the inferior vena cava (MOVC) causing the Budd-Chiari syndrome.

Budd-Chiari syndrome is not synonymous with MOVC. The former is caused by obstruction of the hepatic vein outflow, which can have a variety of causes, only one of which is MOVC. Other causes of Budd-Chiari syndrome are intravascular thrombi, malignancy, polycythemia vera, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, pregnancy, and use of contraceptives [2].

Percutaneous balloon dilation is an effective and safe alternative to surgical treatment of MOVC. My colleagues in China and I (unpublished results) have been successful using dilation in 6 such patients, 2 of whom had previous operations. Not only was the obstruction relieved but all the symptoms including leg edema, ascites, varices, and dyspnea disappeared. Over a follow-up period of 10.2 ± 8.4 months (2 to 20 months) the result is very gratifying.

Whether MOVC should be labeled as "coarctation of inferior vena cava" [3] is a matter of semantics. Balloon dilation has been equally effective for nonoperative treatment of coarctation of the aorta [4].

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Reply

To the Editor:

We agree that Budd-Chiari syndrome is not synonymous with MOVC. An exhaustive list of causes for Budd-Chiari syndrome has been listed in our review [1].

Dilation is certainly a method of treatment for MOVC. Invasive dilation was first introduced by Dr Kimura in 1960 [2]. Finger and various devices have been used. Mishima and associates [3] report six deaths directly attributable to invasive dilations.

Noninvasive dilation is gaining popularity with the availability of better balloons and facilities for imaging. But it is not always safe and effective. It may be impossible to cross a stricture. The stricture may need to be punctured by a Brockenborough catheter [4] followed by dilation. Fatal bleeding can occur. The stasis thrombi below the obstruction can get dislodged into the pulmonary circulation [5]. Heparinization during the procedure followed by urokinase and warfarin treatment for a few weeks has been recommended [6]. Residual or recurrent stenosis can occur [7–10]. Balloon dilation may need to be repeated [7]. To achieve an adequate opening multiple balloons have been used simultaneously [6]. Dilation of associated [10] or isolated [8] stenosis of hepatic vein has also been attempted.

However, despite these problems balloon dilation has given satisfactory relief of symptoms [8, 9, 11, 12]. Immediately after dilation, pulmonary edema should be anticipated in some patients [9] and treated.

The label "coarctation of inferior vena cava" was first suggested by Bennett [13]. We believe that this label is more appropriate than MOVC because it lays emphasis on the constriction of inferior vena cava per se at the site of obstruction. If the narrowing of the inferior vena cava is mild and there is a horizontal thin membrane obstructing the flow, the results of balloon dilation would be excellent. The term "coarctation of inferior vena cava" would caution "balloonists" about the constriction in the vena cava, per se, being the primary lesion with a shelf of tissue or "membrane" merely completing the obstruction, similar to the pathology in coarctation of aorta, and remind them about the dangers of rupture, embolism of stasis thrombi, and residual and recurrent stenosis. Ease and efficacy of dilation, be it stricture of inferior vena cava, coarctation of aorta, or stricture esophagus, would depend on the severity of the stricture and extent of fibrosis.

We complement Professor Chang for his good results after dilation. Longer follow-up data would be of interest.

When dilation, be it invasive or noninvasive, fails, alternatives include dorsal cavoatrial bypass using polytetrafluoroethylene graft and excision with or without patch venoplasty [14].

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Reinforcement of Pulmonary Parenchymal Suture

To the Editor:

The recent article by Fulton and Dickson [1] addresses a surgical technical problem that occasionally may cause serious complications, morbidity, and extended hospitalization of the patient. The use of Dacron or Teflon felt bolsters has belonged for a long time to the surgical armamentarium for enforcing sutures on fragile tearable tissues such as arterial wall, myocardium, lung, and other parenchymatous organs [2, 3]. Fulton and Dickson's con-

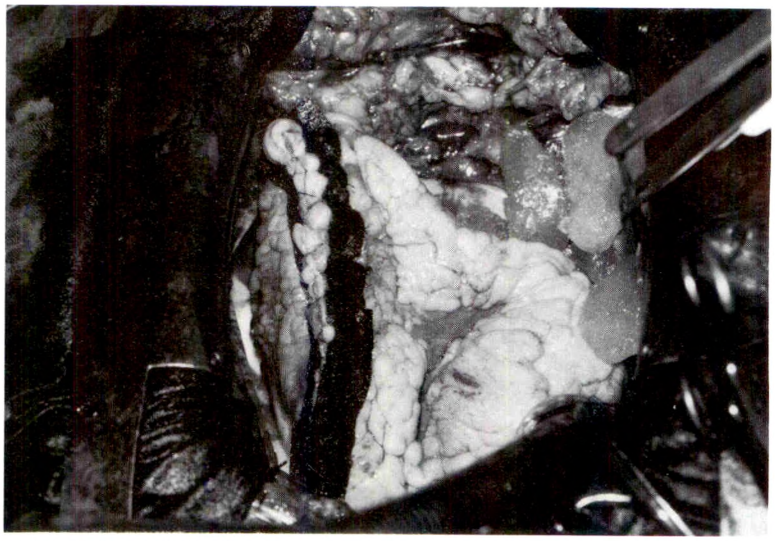

Fig 1. Use of PDS-Vicryl felt as reinforcement of left ventricular suture.

cern regarding placing foreign bodies in apposition to an open airway is real. This is true, not only in the case of pulmonary application; we advocate use of resorbable suture material and, because of its recent availability [4, 5], the use of PDS-Vicryl felt bolsters (Ethicon GmbH, Hamburg, Germany) for all indications (Fig 1) where we used to use Teflon and Dacron felt. Until now in our clinical practice we have not seen any deleterious reactions or problems with this material. In the development of the PDS-Vicryl felt a maximal effort was spent to provide a material allowing tailoring, smoothness, and handling features comparable with those of Dacron or Teflon felt. Furthermore it appears that after resorption the material does not cause firm calcifying adhesions feared during reoperations on patients in whom Dacron or Teflon felt was used previously.

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Inverted Internal Mammary Artery for Myocardial Revascularization

To the Editor:

We read with interest the recent paper by González-Santos and associates [1] on retrograde flow in the distal internal mammary artery (IMA). González-Santos and associates have accurately studied the individual contribution of the terminal branches to the backflow capacity of the distal IMA. They found that the overall flow and diastolic flow component were greater in the musculophrenic than in the superior epigastric artery, suggesting that preservation of musculophrenic and some intercostal arteries is of particular value in providing the distal IMA with adequate backflow in the clinical setting.

A recent paper by our group [2] supports both the findings and the conclusions of González-Santos and associates [1]. In fact, late angiographic patency of an inverted IMA used to bypass a right coronary artery was demonstrated in 1 patient by selective injection of contrast material into an intercostal artery supplying the musculophrenic branch, underlining the importance of the intercostal circulation, rather than the superficial abdominal network, in maintaining an adequate backflow in the IMA.

Furthermore, in agreement with the findings of González-Santos and associates [1], based on our previous [3] and more recent [2] experiences, we also believe that the use of an inverted IMA should be restricted to selected cases, such as patients with completely occluded coronary vessels, to avoid a potential blood steal through the lower-pressure distal IMA. Also, inverted IMA should not be used until the magnitude of retrograde flow has been considered adequate by intraoperative measurement.

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artery (IMA) with retrograde flow for coronary artery grafting. Thorac Cardiovasc Surg 1986;34:204–6.

The First Mitral Valve Replacement

To the Editor:

I wish to report what I believe to be the first mitral cardiac valve replacement in the world, undertaken on July 22, 1955, at the City General Hospital, Sheffield, England, by Mr Judson T. Chesterman. The procedure was for severe mitral valve disease in a 34-year-old man.

Mr Judson T. Chesterman was Consultant Cardiothoracic Surgeon working at the City General Hospital, now called the Northern General Hospital, Sheffield, England. He had a mechanical interest in the automobile internal combustion engine, and his tinkering with car engines led him to try to solve valvar disease by mechanical means.

Mr Chesterman had initially approached the hospital plumber to fashion him a valve in copper to his own design. When this was produced, however, Mr Chesterman was unsure of the choice of material, so a second valve was fashioned. This was hand-made by a Mr Clifford A. Lambourne, now Senior Chief MLSO, in the Department of Histopathology at the Northern General.

Using a sketch given him by Mr Chesterman (Fig 1), and using the material Perspex, he began to make a valve that worked on the principles of a car engine valve. Mr Lambourne had worked with Perspex in his capacity as a pathology technician but he had not had to fashion items on a lathe before. The hospital did not have a delicate lathe, such as a watchmaker would use, and the only one available to Mr Lambourne was a monster 6″ center lathe in the Works Maintenance Department.

It was with great skill that he made the prosthetic mitral valve with such precision. To polish it Mr Lambourne used a silk handkerchief, and as all the work was done in his own time he would take his new wife to the local cinema and spend the time polishing the valve. It took him three films' worth to get the required result!

At operation Mr Judson T. Chesterman made an incision through the fifth intercostal space and continued with a transverse sternotomy stretching from the left to the right side of the patient's chest. The patient was cooled with ice-packs and the use of a wind tunnel. The inferior vena cava and the superior vena cava were clamped to give venous inflow occlusion. The valve was totally excised and the manufactured valve was inserted through the atrium and pushed into the mitral valve orifice. The valve was secured with several sutures and two Perspex buttons on the outside of the heart. The operation was performed on a beating heart, from which air was removed with a syringe and needle. The anesthetist was Dr James Johnston.

The patient survived for 14 hours. Unfortunately, because the valve poppet was shaped the way it was, the up and down movement of the inner disc caused the outer casing to twist out of position, and the valve failed. After the death of the patient, further work on developing the valve ceased. The valve had three components (Fig 2). The outer casing was designed to slip into place in the mitral valve ring, and had two suture holes on opposite sides of the flange through which sutures were passed and led outside the heart. These were tied onto the extracardiac security buttons. The inner surface of the casing was machined as a valve seat, into which the shaped poppet valve could seat. The pistonlike movement of this poppet valve was limited by two "feet" to prevent its escape.

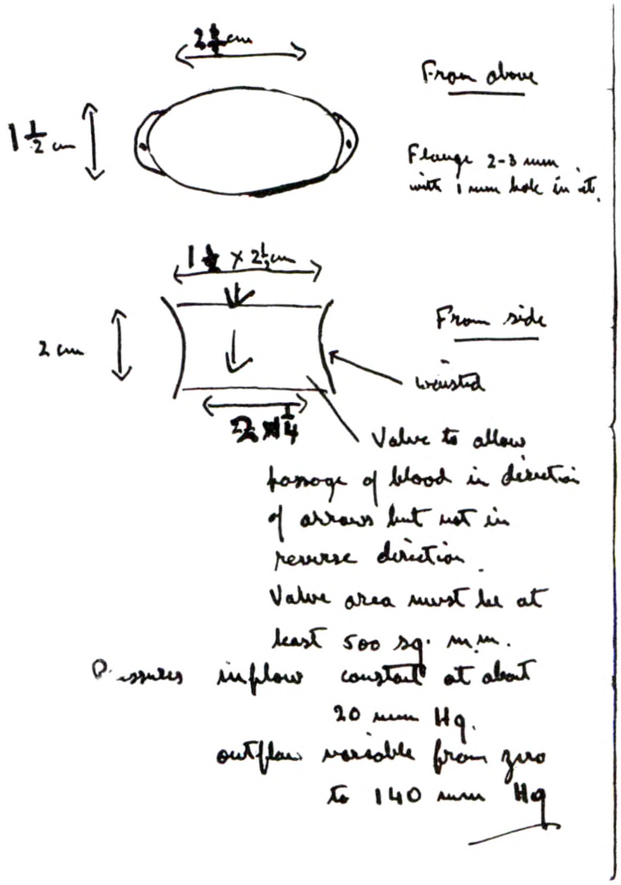
2½ cm
From above
1½ cm
Flange 2-3 mm with 1 mm hole in it.
1½ × 2½ cm
From side
2 cm
waisted
2¼
Valve to allow passage of blood in direction of arrows but not in reverse direction.
Valve area must be at least 500 sq. m.m.
Pressures inflow constant at about 20 mm Hg.
outflow variable from zero to 140 mm Hg

Fig 1. Original sketch for valve design.

Mr Lambourne continued to assist Mr Chesterman in his search for a mitral valve. They had heard of a new material called Teflon but were not allowed the £7.50 by the hospital to purchase some! Mr Lambourne went back to his giant lathe to turn beautiful Perspex spheres, some of which he still has, and which have since proved to be the right idea when the Starr-Edward valves came onto the market.

The original valve, still inside the heart, is preserved in formalin in the Northern General Hospital, Sheffield.

Mr Chesterman has since died at the age of 84 years, and so has Dr Johnston in 1988, both great men in their field.

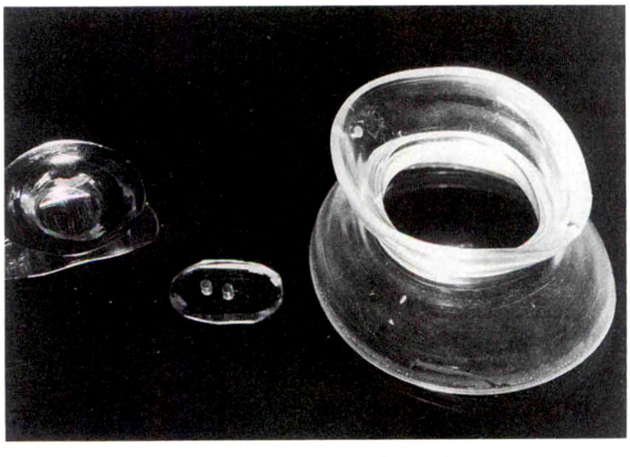

Fig 2. The disassembled mitral Perspex valve: outer casing (right), extracardiac button (center), and poppet valve (left).

Previous attempts at producing an artificial heart valve include those of Charles P. Bailey and William Likoff [1] who had presented a paper on April 18, 1952, based on 15 early attempts to correct aortic insufficiency by the placement of a pedunculated ball or hammock of pericardial tissue within the valve. This prosthesis was made by rolling nylon fabric into a small ball, 1 cm in diameter, the resulting structure closely resembled a polliwog or tadpole. In the belief that a perfectly smooth structure such as a sphere of silicone rubber might be preferable to a soft mass of nylon, the polliwog valve was redesigned in silicone and made in several sizes, but was never used in a human subject. They were known as Neuman valves. On September 11, 1952, it was reported [1] that Charles Hufnagel had placed a methyl methacrylate ball-valve prosthesis in the descending aorta for the treatment of aortic regurgitation.

The Sheffield valve described in this letter differs in being the first truly intracardiac valve replacement performed on a human subject.

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Hemolysis After Valve Repair

To the Editor:

Wilson and associates [1] reported on 2 patients in whom severe hemolysis developed after mitral valve repair and annuloplasty using a Duran ring. They noted that review of the literature disclosed a total of 6 patients with postoperative hemolysis after mitral valve repair, of whom 3 had placement of an annuloplasty ring. We wish to report 1 additional patient whom we treated for mitral insufficiency and in whom a severe hemolytic anemia developed after mitral valve repair and Duran ring annuloplasty.

Severe breathlessness on exertion developed in a 56-year-old male construction worker over a 6-month period. Diagnostic investigations with echocardiography and Doppler testing demonstrated severe mitral regurgitation with a flail posterior leaflet. Preoperative angiography identified 3 to 4+ mitral regurgitation and normal coronary arteries.

At operation, myxomatous degeneration of the mitral valve was noted with prolapse of the middle scallop of the posterior leaflet and ruptured chordae; quadrangular resection was carried out with an annuloplasty using a No. 29 Duran ring. Three months postoperatively a severe hemolytic anemia was observed with schistocytes seen on peripheral blood smear and depressed haptoglobin and hemoglobin indices (0.4 g/L and 56 g/L). Repeat echocardiography, Doppler echocardiography, and angiography revealed only a 1+ mitral regurgitant jet. The anemia was refractory to iron and folate supplements and treatment required repeated blood transfusions. Mitral valve replacement was advised for long-term management.

At reoperation, the Duran ring was well seated and the posterior leaflet repair appeared intact. There was an area of poor endothelialization on the posterior portion of the ring, which may have resulted from a posteriorly directed jet of residual regurgitation (although mild). Mitral valve replacement with a St. Jude bileaflet mechanical prosthesis was performed. The patient's postoperative course was uneventful with prompt resolution of the hemolytic anemia.

Enthusiasm for mitral valve repair in the setting of myxomatous disease has developed in many centers, with surgeons citing a lower morbidity in reparative procedures than observed with valve replacement. Our experience reinforces the prior observation of Wilson and associates that a hemolytic syndrome can be associated with well-seated cloth-covered rings. This is likely due to an incomplete repair with residual regurgitation, albeit mild. We believe the resection/suture line retracted somewhat during healing, allowing the anterior leaflet to overlap and create an isolated, posteriorly directed, regurgitant jet. Cardiac hemolysis is an unusual postoperative complication of valve operations; however, those surgeons performing valve repair are advised to bear in mind the association of an annuloplasty ring with this hematologic problem.

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Reference

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CORRECTION

"Cancer Recurrence After Resection: T1 N0 Non–Small Cell Lung Cancer"

by Paul Thomas, MD, Lawrence Rubenstein, PhD, and the Lung Cancer Study Group (Ann Thorac Surg 1990;49:242–7)

The Editorial Office has received a communication from the senior author that there are errors in the figures. In Figures 1 and 3, under "HISTOLOGY," the numbers of patients should be as follows: Squamous, 312 (not 92); Nonsquamous, 595 (not 119); and All Patients, 907 (not 201). Also, in Figures 3 and 4, the x axis should be labeled "Percent Surviving Without Recurrence."

Southern Thoracic Surgical Association Rules for Submission of Abstracts

Abstracts for papers to be presented for the 1991 Annual Meeting are now being accepted. The deadline for postmark of abstracts is May 15, 1991. An original and 1 copy should be submitted, using the official Association abstract form, to Frederick L. Grover, MD, Chairman, Program Committee, The Southern Thoracic Surgical Association, 401 North Michigan Ave, Chicago, IL 60611-4267. Additional forms are available upon request from the Association.

Abstracts must summarize an original contribution not presented or accepted for presentation elsewhere. *Abstracts received after the deadline will not be considered.* The information requested at the bottom of this form must be completed indicating who is to receive the notice of acceptance or rejection and who will present the paper if accepted.

Abstracts may be submitted for the regular program, the Forum, or either. Papers selected for the Forum will be published in *The Annals of Thoracic Surgery* if they pass the usual editorial review.

Essayists are reminded that all papers accepted for presentation must be submitted in triplicate to Hendrick B. Barner, MD, Secretary-Treasurer, at the time of presentation or to the Editor of *The Annals of Thoracic Surgery* prior to presentation.

Abstracts frequently obscure the value of their content because they are poorly organized. It is important that methods and results be clearly defined in the abstract; general statements such as "results will be presented" are not acceptable. When a procedure or method is stated to have "advantages," those advantages should be defined. Abstracts that simply summarize results without defining objectives and methods are equally undesirable.

Presentations in the regular program are limited to 10 minutes; those in the Forum are limited to 5 minutes.

In discussion of papers, the Association encourages a healthy spirit of constructive critical review and rebuttal by comments pertinent to the content of the paper being presented. Presentation of the discussion in the form of "secondary papers" will not be welcomed.

INSTRUCTIONS FOR ABSTRACTS

The official abstract form or photocopies must be used. **Authors must indicate whether they want the abstract considered for the regular program, the Forum, or either by checking the appropriate box. Authors must also categorize the principal subject of their abstract by checking the appropriate box.**

1. Title of abstract must be completely CAPITALIZED.
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3. Indicate each author who is a member of the Southern Thoracic Surgical Association with an asterisk following the name.
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    c. A summary of the results and/or conclusions of the study, including sufficient details to support those conclusions.
    d. A statement concerning the significance and implications of the work.
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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information.

Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Second Scientific Meeting of the International Association for Cardiac Biological Implants, Washington, DC—May 5, 1991

The topic of this meeting, dedicated in memory of the late Donald Magilligan, MD, will be infective endocarditis of heart valves. For information on this meeting, contact Dr Shlomo Gabbay, Office of the Secretary, UMDNJ, Department of Surgery, Room G502, 100 Bergen St, Newark, NJ 07103.

Seventy-first Annual Meeting of The American Association for Thoracic Surgery, Washington, DC—May 6–8, 1991

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Thoracic Imaging 1991, Toronto, Canada—May 13–17, 1991

This meeting is sponsored by The Society of Thoracic Radiology. For information on this meeting, contact Dawne Ryals, Ryals and Associates, PO Box 1925, Roswell, GA 30077-1925; or telephone (404) 641-9773 (facsimile: (404) 552-9859).

Quality of Life After Open Heart Surgery, Antwerp, Belgium—May 16–18, 1991

This meeting is sponsored by The World Health Organization, the European Society of Cardiology, and the International Society and Federation of Cardiology. For information on this meeting, contact P. J. Walter, MD, FACS, Professor and Chairman of the Department of Cardiovascular Surgery, University Clinic of Antwerp, B 2520 Antwerp, Wilrijkstraat 10, Belgium; or telephone 00323.829.11.11 (facsimile: 00323.830.20.99).

Vascular Surgery 1991—Current State of the Art, New York, New York—May 16–18, 1991

For information on this meeting, contact Ann J. Boehme, CMP, Associate Director for Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042; or telephone (718) 470-8650.

Coronary Surgery: Clinical and Basic Perspectives, Sheffield, England—May 17, 1991

For information on this meeting, contact G. D. Angelini, Clinical Sciences Centre, Northern General Hospital, Herries Rd, Sheffield S5 7AU, England.

Surgery for Coronary Artery Disease, Durham, North Carolina—May 20–21, 1991

For information on this meeting, contact Vanessa Moore, PO Box 2986, Duke University Medical Center, Durham, NC 27710, or telephone (919) 684-6077; or contact American College of Cardiology, Extramural Programs Department, 9111 Old Georgetown Rd, Bethesda, MD 20814, or telephone (800) 253-4636.

Fifth International Symposium on Cardiac Bioprostheses, Avignon, France—May 24–27, 1991

This meeting is sponsored by the Scientific Committee for the Advancement of Cardiac Bioprostheses. For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870.

Fourth International Symposium on Echocardiography and Doppler in Cardiac Surgery, Innsbruck, Austria—May 27–29, 1991

For information on this meeting, contact G. Maurer, MD, or W. Mohl, MD, PhD, c/o Interconvention, A-1450

Vienna, Austria; or telephone +43/1/23 69/2642 (telex: 11 18 03; facsimile: +43/1/23 69/648).

Ninth World Symposium on Cardiac Pacing and Electrophysiology, Washington, DC—May 28–31, 1991

This meeting will incorporate the Twelfth Annual Scientific Session of the North American Society of Pacing and Electrophysiology. For information on this meeting, contact IXth World Symposium Secretariat, c/o NASPE, 377J Elliot St, Newton Upper Falls, MA 02164; or telephone (617) 237-1866 (facsimile: (617) 431-1991).

Coronary Artery Surgery and Esophagus Cancer in ARGE ALP and PENTAGONALE, Salzburg, Austria—May 30–June 1, 1991

For information on this meeting, contact Prof Dr Felix Unger or Prof Dr Peter Brücke, c/o Interconvention, Austria Center, Vienna A-1450, Austria; or telephone 43/1/23 69/26 43 (facsimile: 43/1/23 69/648).

The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Boston, Massachusetts—June 3–5, 1991

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Cardiac Arrhythmia Surgery International Seminar II, Geneva, Switzerland—June 12–14, 1991

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870 (facsimile: (714) 759-6911).

Seventeenth Annual Meeting of The Western Thoracic Surgical Association, Seattle, Washington—June 26–29, 1991

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Second International Seminar on Transplantation for End-Stage Lung Disease, Zurich, Switzerland—June 27–28, 1991

For information on this meeting, contact A.K.M. Congress Service, Clarastrasse 57, Ch 4005 Basel, Switzerland; or telephone 061-691-8888 (facsimile: 061-691-8189).

Techniques in Pulmonary and Oesophageal Surgery, Liverpool, England—July 14–16, 1991

For information on this meeting, contact Mr R. J. Donnelly, The Cardiothoracic Centre, Broadgreen Hospital, Thomas Dr, Liverpool L14 3LB, England; or telephone 051 228 4878 (facsimile: 051 220 8573).

Twentieth World Congress of The International Society for Cardiovascular Surgery, Amsterdam, the Netherlands—September 1–6, 1991

For information on this meeting, contact the Registrar: XX World Congress—ISCVS, International Travel Service, Inc, 104 Wilmot Rd, Suite 300, PO Box 825, Deerfield, IL 60015; or telephone (708) 940-2100 (facsimile: (708) 940-2386); or contact the Congress Secretariat, International Society for Cardiovascular Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

Current Issues in Thoracic Organ Transplantation, Essen, Germany—September 19–21, 1991

For information on this meeting, contact Organizing Secretariat, Gisa Brodde Meetings, Saalbau Essen, PO Box 100301, D-4300 Essen 1, Germany; or telephone (0)201-232121 (facsimile: (0)201-232273).

Heart Valve Replacement—Past Performance: Future Prospects, Sheffield, United Kingdom—September 19–21, 1991

For information on this meeting, contact Jenny Pupius, Symposium Secretariat, Department of Medical Physics and Clinical Engineering, Royal Hallamshire Hospital, Glossop Rd, Sheffield S10 2JF, United Kingdom; or telephone (0742) 555250 (facsimile: (0742) 729981).

Fifth Annual Meeting, European Association for Cardio-Thoracic Surgery, London, United Kingdom—September 22–25, 1991

For information on this meeting, contact Organising Secretariat, Conference Associates & Services, Ltd, Congress House, 55 New Cavendish St, London W1M 7RE United Kingdom; or telephone 071 486 0531 (facsimile: 071 935 7559; telex: 934 346 CONFAS G).

Fifth Annual Meeting of the Mediterranean Association of Cardiology and Cardiac Surgery, Alexandria, Egypt—September 23–27, 1991

For information on this meeting, contact Prof M. El-Fiky, Chairman, Cardiac Surgery Department, Ain Shams Faculty of Medicine, Abbassia, Cairo, Egypt; or telephone (202) 834981 or (202) 835495 (facsimile: (202) 834981).

Third Combined Meeting of the Nederlandse Vereniging Voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie, Maastricht, the Netherlands—November 7–9, 1991

For information on this meeting, contact Organizing Secretariat, Conference Agency Limburg, Mrs Brigitte Bessems, c/o University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, the Netherlands; or telephone 31 (0)43 258344 (facsimile: 31 (0)43 258355).

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Arthur Carlucci, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010 (telephone: (212) 633-3806; facsimile: (212) 633-3880). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.25 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $17.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3853). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

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SITUATIONS AVAILABLE

Cardiovascular surgeon, board certified/eligible, wanted to join two surgeons in an established cardiovascular program in the southeastern USA. Must have experience in adult cardiac, thoracic, and vascular surgical procedures. Salary/full partnership negotiable. Please send resume.

Please respond to Box 398. 398C/H

Thoracic/vascular surgeon needed to join prominent, active 3-man group in desirable suburban community in greater NY metropolitan area. Excellent opportunity for well-trained, highly motivated individual. Recent graduate preferred. Possible academic affiliation. Please respond with CV.

Please respond to Box 404. 404J/C

Cardiac surgeon—board certified/eligible to be third member of established practice in suburb of Washington, DC, expanding to second hospital. Excellent compensation and benefits. Great opportunity for recent graduate wishing to locate in area of nation's capital. Practice focus is primarily in adult cardiac surgery with additional work in thoracic and peripheral vascular surgery available.

Please send curriculum vitae to PO Box 34945, Bethesda, MD 20817. 415J/C

Cardiothoracic/vascular surgeon: board certified in general and thoracic surgery. Minimum of 2 years of practice experience. Very active private multispecialty practice. Located in western Pennsylvania. Salary leading to full partnership. Excellent benefits. Detailed CV must accompany response. All replies treated confidentially.

Please respond to Box 419. 419J/C

Cardiovascular-thoracic surgeon—BE/BC to join established and growing 2-surgeon group in northeastern US. Practice includes high volume cardiac and general thoracic surgery. Recent trainee preferred. Submit CV.

Please reply to Box 423. 423J/C

Cardiac surgeon wanted to join established private practice in upstate New York, primarily adult cardiac. Board certified or eligible required. New or recent graduate preferred. Please send CV and references.

Please respond to M. A. Marvasti, MD, 101 Union Ave, #813, Syracuse, NY 13203. 429K/D

Wanted: BE/BC general surgeon with interest and experience in thoracic surgery who enjoys general surgery, or non-cardiac thoracic surgery, to assume practice of retiring double-boarded thoracic/general surgeon. 34-member multispecialty group in dynamic area hub city of 35,000, with six satellite offices in strategic locations and referral area of 300,000 plus. Superb hospital facilities, including CT, MRI, cardiac surgery, neurosurgery, etc. Directed towards those concerned about quality family lifestyle and professional concerns.

Contact Recruitment Coordinator, Park Clinic, 890 North Eisenhower Ave, Mason City, IA 50401; or dial 800-798-4321 for more information. 431K/D

Cardiovascular/vascular surgeon wanted to join busy established adult practice in Ohio. Recent graduate preferred. Please submit curriculum vitae. Association will lead to partnership.

Please respond to Box 436. 436K/C

BC/BE adult cardiothoracic surgeon wanted to join active established department in large multispecialty group practice located in metropolitan Midwest community. Medical school affiliation available. Respond with curriculum vitae.

Please respond to Box 437. 437K/D

Minneapolis cardiothoracic/vascular group seeks to add fifth surgeon, BC/BE.

Respond to BLH Physician Search, 2231 Lee Ave N, Minneapolis, MN 55422; (612) 588-1116 or -0333. 438L/E

Board certified/eligible cardiothoracic surgeon for busy 1-physician practice in Atlanta. Transplant experience. Future partnership.

Send resume to Georgia Cardiac Surgical Association, PO Box 491203, College Park, GA 30349. 439L/E

Thoracic and vascular surgeon needed—Southeast: Looking for a partner to join an established surgeon to practice noncardiac thoracic and vascular surgery in mid-sized city. Must be board certified or eligible. No buy-in needed, guaranteed income available. Excellent community to raise a family with the cultural advantages of a large city but not the hassles. Will consider others, but recent graduate preferred. Send CV, and include description of interests, and career goals.

Please respond to Box 454. 454L/C

Cardiothoracic surgeon interested in joining an established practice in the Southwest. Must be experienced in adult cardiac, pulmonary, and vascular surgery. Must be board certified/board eligible. Please respond with curriculum vitae.

Please respond to Box 457. 457L/C

Cardiovascular and thoracic surgeon, BE/BC, to join another physician in a rapidly expanding private practice located in the Southeast. Please send curriculum vitae and references.

Please respond to Box 459. 459L/E

University of Massachusetts Medical Center is recruiting candidates for its newly opened Cardiothoracic Surgical Residency

Program for 1991, 1992, and 1993. The applications for the 1993 position will be processed through the Match Program for Cardiothoracic Residencies.

Request applications from and submit curriculum vitae and three letters of recommendation to Thomas J. Vander Salm, MD, Chief, Division of Cardiothoracic Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655; telephone: (508) 856-2216. 462L/E

Cardiovascular surgeon to join another physician in partnership. Lucrative practice opportunity. *Must do* comprehensive cardiovascular *and* thoracic procedures. On staff at five major hospitals. Two offices and staff in place. Must be able to establish new lines of referral. State-of-the-art pacemaker clinic in office. Suburban location near Chicago, IL (population of 5 million) is 25 minutes due west of downtown. $175,000 first year salary plus pension, buy-in, and other benefits.

Send CV or call Greg Stelmach, Jackson and Coker, Inc, 115 Perimeter Center Place, Suite 380 10031, Atlanta, GA 30346; telephone: 1-800-544-1987. 467A/C

Assistant/Associate Professor needed for expanding *cardiothoracic surgery* program. Position involves primarily adult cardiac surgery with some thoracic. Experience/interest in electrophysiology advantageous. Commitment to research and teaching essential. Exceptional opportunity for academic development in a desirable community. USF is an EEO/AA employer.

Please send CV to Peter P. McKeown, Chief of Cardiovascular & Thoracic Surgery, University of South Florida, #730, 4 Columbia Dr, Tampa, FL 33606. 469A/C

Cardiac surgeon, board certified. Minimum 5 years experience in adult cardiac surgery to join 2-surgeon practice in Southeast. Send CV.

Please respond to Box 471. 471A/C

Cardiothoracic/vascular surgeon, BE/BC, wanted to join growing practice in New Jersey. Recent graduate preferred. Please respond with CV.

Please respond to Box 477. 477A/C

Thoracic and vascular surgeon, board certified, to join active (noncardiac) thoracic and vascular practice in northern New Jersey. Competitive salary and benefits. Please respond with curriculum vitae.

Please respond to Box 481. 481A/C

Cardiothoracic surgeon, BC/BE, to join an extremely busy and rapidly expanding solo practice of predominately adult cardiac surgery in a medium-size southern city serving as a regional referral center. Unusually high quality medical care in this outstanding community. Excellent opportunity for a new or recent graduate with generous compensation package leading to early partnership. Please send CV.

Please respond to Box 482. 482A/C

Cardiovascular and thoracic surgeon, BE/BC, wanted to join a busy private practice in Pittsburgh, PA. Please respond with curriculum vitae and details of experience.

Please respond to Box 483. 483A/C

Cardiothoracic surgeon, BE/BC, to join busy 1-man private practice in Dallas. Excellent opportunity. Salary leading to partnership. Please send CV and references.

Respond to Practice Enhancement Resources, PO Box 655999, Dallas, TX 75265; Attention: Carol. 487B/D

Pacific Northwest—Adult cardiothoracic surgeon, board certified, to join established surgeon in growing private practice. Quality medicine in an outstanding area. Early full partnership.

Please respond to Box 488. 488B/C

Cardiovascular and thoracic surgeon to join established 3-man private practice in mid-South. Practice includes thoracic, cardiac, and vascular surgery. Must be board certified or eligible in thoracic and cardiovascular surgery. Prefer candidate who has recently completed his/her training. Please respond with curriculum vitae.

Please respond to Box 489. 489B/G

A busy greater Boston cardiothoracic surgical group seeks to add a third surgeon as soon as possible. This practice operates from a multihospital referral base. Candidate must be BE/BC. Excellent salary and benefit package. Please respond with CV.

Please respond to Box 490. 490B/D

Cardiothoracic surgeon, board eligible or certified, recent training preferred. University practice, salaried position. Applicant must have experience with cardiac transplantation, pediatric cardiac surgery, and both pulmonary and esophageal surgery. Please send curriculum vitae.

Please respond to Box 495. 495B/C

Immediate opening for cardiothoracic surgeon for active practice of adult cardiac and general thoracic surgery in lovely seaside south Florida community. Must be mature, congenial, board-eligible individual with access to Florida license.

Please respond to Box 496. 496B/C

Cardiothoracic surgeon, BE/BC, wanted to join 2 surgeons in busy and expanding practice on the West Coast. Experience or training in adult cardiac surgery, thoracic surgery, pacemaker surgery, valve repair, and arrhythmia surgery necessary. Position available July 1991; new or recent graduate preferred. Excellent salary and benefits with eventual partnership possible. Send curriculum vitae and references.

Please respond to Box 497. 497C/E

PA-C wanted for established, growing, private practice in adult and pediatric cardiothoracic surgery. Five surgeons, five PAs. Near San Francisco. Excellent benefits. Salary negotiable. Prefer experienced CT PA, but will train the right person.

Send CV to Coyness Ennix, MD, 365 Hawthorne Ave, Suite 301, Oakland, CA 94609-3102. 499C

Clinical associate: a very busy adult cardiac surgery practice located in northeast Philadelphia is seeking an ABTS eligible or certified clinical associate.

Submit inquiries and CV to John Bell-Thomas, MD, Chairman, Division of Cardiothoracic Surgery, Albert Einstein Medical Center, 5501 Old York Rd, Philadelphia, PA 19141. 501C

Cardiovascular surgeon wanted to join a 2-man group in an established practice in the Southeast. Would prefer a recent graduate, but all applications considered. Generous salary leading to partnership. Practice includes all aspects of adult cardiac, thoracic, and vascular surgery. Send curriculum vitae with experience and recommendations.

Please respond to Box 502. 502C/E

Cardiothoracic surgeon to join group of two, in Michigan. Please respond with CV and references.

Please respond to Box 504. 504C/H

Thoracic surgeon, BC/BE, needed to join two others in a busy thoracic surgical practice without open heart surgery. Located in a prime suburb of NYC with a good quality of life. Rapid partnership advancement. Recent graduate preferred. Please reply with a curriculum vitae.

Please respond to Box 505. 505C/D

Cardiothoracic surgeon needed for established cardiac program in the Philadelphia area. Must be BE/BC. New or recent graduate preferred. Salary leading to partnership.

Please send CV to Ms Rosemary Morrone, Administrator, Department of Surgery, 3 Cooper Plaza, Suite 411, Camden, NJ 08103. 506C

Cardiothoracic surgeon—second surgeon needed for 200 pump adult cardiac surgery practice in Rocky Mountain region. Salary plus bonus leading to partnership after third year. Send curriculum vitae and references.

Please respond to Box 507. 507C/D

Cardiac surgeon with 3 to 5 years experience in adult cardiac surgery wanted for immediate opening in Northeast. Program now doing 30 to 40 cases/month and senior surgeon needs an experienced #2 individual for long-term commitment. Excellent salary leading to partnership. Reply with curriculum vitae.

Please respond to Box 508. 508C/E

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to Box 509. 509C/H

General thoracic surgeon: the Department of Surgery and the Section of Thoracic Surgery invite applications and nominations for a faculty position in general thoracic surgery at the Assistant or Associate Professor level at the University of Chicago. Prospective candidates should be American Board of Thoracic Surgery eligible or qualified as of July 1, 1991, have demonstrated excellence in clinical surgery and research, and possess a commitment to teaching. Preference will be given to those who have broad experience in general thoracic surgery, including lung transplantation. The successful candidate is expected to develop his/her own research program.

Applicants should have their curriculum vitae and two letters of recommendation sent to Dr Mark Ferguson, Chief, Section of Thoracic Surgery, The University of Chicago, Box 255, 5841 Maryland, Chicago, IL 60637; facsimile: (312) 702-5909. Applications must be received by June 1, 1991. The University of Chicago and its Medical Center are affirmative action/equal opportunity employers. 510C/E

Cardiovascular surgeon to join a young diplomate, ABTS, in a practice that has grown to some 600 hospital surgeries per year. Location is in a city in the mid-South. The only open heart program in 15 counties. 325-bed regional medical center, 2 catherization labs. Practice consists of cardiac, thoracic, and vascular surgery. Full financial support including productivity incentive. All benefits, malpractice and office expenses provided.

Please respond to Box 511. 511C

Cardiovascular surgeon: we are looking for a recently trained B/E or B/C CV surgeon to join our very busy and enjoyable 2-man Cardiovascular Department at Billings Clinic, a progressive major regional multispecialty clinic in the northern Rocky Mountain region. This is an outstanding practice opportunity for the right individual seeking a challenging and rewarding surgical practice in surroundings conducive to the highest quality of living for the surgeon and his or her family.

For further information, please call (406) 256-4766 or forward CV to Ann B. Oglesby, MD, MDA, Medical Director, Billings Clinic, PO Box 35100, Billings, MT 59107-5100. 512C/E

Academic institution with private hospital affiliation seeks recent graduate who is board certified or board eligible ABTS for a clinical position as a cardiothoracic surgeon. Applicant should have an interest and expertise in pulmonary and cardiac transplantation as well as teaching.

Please send curriculum vitae to Tom D. Ivey, MD, Department 0251, Cincinnati, OH 45263. 515C/D

Academic cardiothoracic surgeon: the Division of Cardiothoracic Surgery at the University of Massachusetts is expanding its academic faculty. Candidates will be expected to have an interest in developing an active cardiothoracic practice, to participate in thoracic and general surgical residency training, and to take part in clinical and/or laboratory research. The University of Massachusetts is an equal opportunity employer.

Please respond with curriculum vitae to Thomas J. Vander Salm, MD, University of Massachusetts Medical Center, 55 Lake Ave, North, Worcester, MA 01655. 516C/E

SITUATIONS WANTED

Cardiovascular and thoracic surgeon, 39, ABS, ABTS, excellent technique and results, personable. Seeks opportunity with new program or group practice.

Please respond to Box 468. 468A/D

Cardiothoracic and vascular surgeon, 44, ABS, ABTS wishes to relocate. Extensive experience in cardiac, thoracic, and vascular surgery. Would be interested in starting new program or association with established practice. Curriculum vitae and references upon request.

Please respond to Box 479. 479A/C

Cardiovascular and thoracic surgeon wishes to relocate. University trained, 38, hard working, experienced in all important aspects of adult cardiac, general thoracic, and vascular surgery.

Please respond to Box 484. 484B/C

FELLOWSHIPS

Fellowship in cardiovascular surgery for 1 year available January 1 or July 1 with group doing approximately 1,000 cardiac procedures per year and large volume of vascular procedures. ABS eligible or certified, California medical license required or readily obtainable. Ideal for a person between general surgery residency and thoracic surgery residency.

Please respond with curriculum vitae to Bradley J. Harlan, MD, 5301 F Street, Suite 312, Sacramento, CA 95819. 480A/F

Fellowship in pediatric cardiovascular surgery available July 1991. Experience includes surgery for hypoplastic left heart syndrome and arterial switch. A large, well-organized collection of heart specimens available for review. Illinois license or equivalent required. Salary and benefits in the high $40s.

Please respond to Division of Pediatric Cardiac Surgery, The Heart Institute for Children, Christ Hospital and Medical Center, 4440 W 95th St, Oak Lawn, IL 60453. 443L/C

Surgical residents/fellows—Clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart & Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, ext. 359. 445L/C

A 2-year Cardiovascular Research Fellowship position is available 7/1/91 in the Division of Cardiothoracic Surgery at the University of Massachusetts Medical Center. This is an opportunity for a closely supervised and highly productive cardiac research experience. Requirements: (1) A minimum of 2 years of surgical training; (2) a commitment from an institution to complete the applicant's training in general surgery; (3) intentions to pursue an academic career in cardiothoracic surgery.

Interested candidates should contact Marc S. Visner, MD, Division of Cardiothoracic Surgery, University of Massachusetts Medical Center, 55 Lake Ave North, Worcester, MA 01655; telephone: (508) 856-2975. 461L/E

Cardiac surgical fellowship available at medical center doing a large volume of adult cardiac surgical procedures; program affiliated with the University of Miami, Florida. Medical license necessary, ideal for board eligible/certified general surgeon awaiting thoracic residency or board-eligible individual in thoracic surgery seeking additional experience.

Please respond with CV to Donald B. Williams, MD, Department of TCVS, Mount Sinai Medical Center, Miami Beach, FL 33140. 473A/C

Private practice fellowship in a very busy adult and pediatric cardiac surgical and transplant/artificial heart program. The fellowship terms can be negotiated. Must be in general or thoracic surgery training. Iowa license required.

Please respond to Box 486. 486B/C

Cardiac surgical fellowship at Baystate Medical Center, Springfield, Massachusetts: 2-year appointment beginning July 1, 1991. Salary commensurate with training and consistent with hospital scale. One year intensive exposure and experience opportunity in adult cardiac surgery and 1 year intensive research exposure in myocardial ischemia and preservation. PG-5 or beyond. Interview and references required.

For more information please write Richard M. Engelman, MD, Chief, Cardiac Surgery, Baystate Medical Center, Springfield, MA 01199. 498C/D

Clinical fellowship in adult cardiothoracic surgery available July 1, 1991. Fellowship experience will include acquired cardiac, general thoracic, pulmonary, and esophageal surgery. Minimum requirement: American Board of Surgery eligibility or certification. Competitive salary and benefits package offered. Please send resume.

Please respond to Box 500. 500C

Fellowship in adult cardiac surgery available for 1 or 2 years in private program performing over 600 open heart procedures yearly. General surgery training required. ECFMG and visa qualified foreign applicants accepted.

Send curriculum vitae to Donald R. Kahn, MD, 817 Princeton Ave, Suite 300, Birmingham, AL 35211. 503C/D

Fellowship in cardiovascular surgery available July 1, 1991. High-volume program with outstanding Fellow involvement and training. Excellent salary and benefits. American Board of Surgery eligibility required.

Please contact M. Terry McEnany, MD, Kaiser Foundation Hospital, 2350 Geary Blvd, San Francisco, CA 94115; (415) 929-5499. 513C/H

Fellowship in cardiothoracic and vascular surgery available July 1, 1991. Program includes over 400 open heart surgery cases and 200 thoracic or vascular procedures. New Jersey medical license required. Good salary and benefits.

Please contact Arthur J. Roberts, MD, Director, Jersey Shore Heart Institute, PO Box 1143, Neptune, NJ 07753. 514C/E

Cardiovascular research fellowship is available for 1 year at the Lahey Clinic beginning July 1, 1991. Prior experience in large animal research, particularly porcine models, is preferable but not mandatory.

Please contact Warren Williamson, MD, Department of Thoracic and Cardiovascular Surgery, Lahey Clinic Medical Center, 41 Mall Rd, Burlington, MA 01805; (617) 273-8340. EOE. 517C

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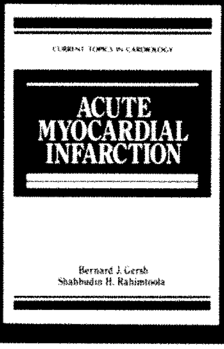

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Please send curriculum vitae to Ms. J. Simkins, Royal Brompton National Heart and Lung Hospital (Chelsea), Sydney Street, London SW3 6NP, England.

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The Surgery Branch of the National Cancer Institute, National Institutes of Health has an immediate opening for a Fellowship in Thoracic Surgery. This program offers a broad experience in thoracic oncologic surgery with opportunities to participate in clinical and basic research. A two to three year program is available for candidates, including benchwork research experience. Applicants must be Board Eligible or Certified in Thoracic Surgery. Please submit a current curriculum vitae and bibliography. Salary for this Fellowship position is dependent on background and qualifications.

Contact:

**Harvey I. Pass, M.D.
Head, Thoracic Oncology Section
Surgery Branch
National Cancer Institute
9000 Rockville Pike
Bldg. 10, Room 2B07
Bethesda, Maryland 20892
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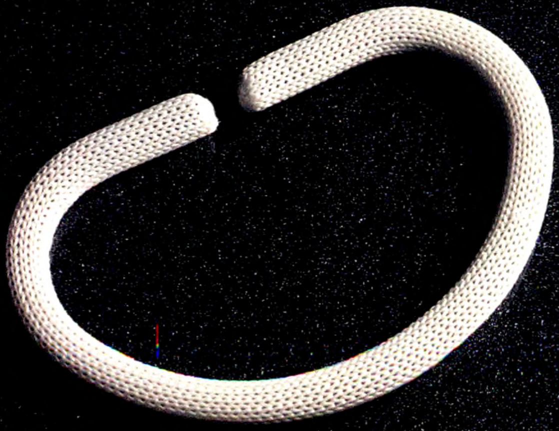

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